Djamila Marlit Salena Wehling

Licenciada em Ciências da Engenharia Química e Bioquímica

Technical optimization of the synthesis of flavours

Dissertação para obtenção do Grau de Mestre em
Engenharia Química e Bioquímica

Orientador: Prof. Dr. Thomas Rödel, Professor Catedrático, Hochschule Merseburg

Co-orientador: Prof. Mário Eusébio, Professor Auxiliar, FCT/UNL

Júri:

Presidente: Prof. Isabel Fonseca, Professor Associado, FCT/UNL

Arguente: Prof. Paula Branco, Professor Auxiliar, FCT/UNL

FACULDADE DE CIÊNCIAS E TECNOLOGIA
UNIVERSIDADE NOVA DE LISBOA

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Título

“No amount of experimentation can ever prove me right, a single experiment can prove me wrong”

Albert Einstein

Acknowledgement

This project, consuming a huge amount of work and research, as well as effort and dedication not only from myself but from all my tutors, would not have been possible without the support and help from all the people involved. For that sense, I would like to express my sincere gratitude to everyone, as mentioned.

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Abstract

The goal of this thesis is the investigation and optimization of the synthesis of potential fragrances. This work is projected as collaboration between the University of Applied Sciences in Merseburg and the company Miltitz Aromatics GmbH in Bitterfeld-Wolfen (Germany).

Flavoured compounds can be synthesized in different ways and by various methods. In this work, methods like the phase transfer catalysis and the Cope-rearrangement were investigated and applied, for getting a high yield and quantity of the desired substances and without any by-products or side reactions. This involved the study of syntheses with different process parameters such as temperature, solvent, pressure and reaction time. The main focus was on Cope-rearrangement, which is a common method in the synthesis of new potential fragrance compounds. The substances synthesized in this work have a hepta-1,5-diene-structure and that is why they can easily undergo this [3,3]-sigma tropic rearrangement.

The lead compound of all research was 2,5-dimethyl-2-vinyl-4-hexenenitrile (Neronil). Neronil is synthesized by an alkylation of 2-methyl-3-butenenitrile with prenylchloride under basic conditions in a phase-transfer system. In this work the yield of isolated Neronil is improved from about 35% to 46% by according to the execution conditions of the reaction. Additionally the amount of side product was decreased. This synthesized hexenenitrile involved not only the aforementioned 1,5-diene-structure, but also a cyano group, that makes this structure a suitable base for the synthesis of new potential fragrance compounds.

It was observed that Neronil can be transferred into 2,5-dimethyl-2-vinyl-4-hexenoic acid by a hydrolysis under basic conditions. After five hours the acid can be obtained with a yield of 96%. The following esterification is realized with isobutanol to produce 2,5-dimethyl-2-vinyl-4-hexenoic acid isobutyl ester with quantitative conversion. It was observed that the Neronil and the corresponding ester can be converted into the corresponding Cope-product, with a conversion of 30 % and 80%. Implementing the Cope-rearrangement, the acid was heated and an unexpected decarboxylated product is formed.

To achieve the best verification of reaction development and structure, scrupulous analyses were done using GC-MS, ^{1}H-NMR and ^{13}C- NMR.

Keywords: Fragrances, Phase-transfer catalysis, Hydrolysis, Esterification, Cope-rearrangement

Zusammenfassung

Die Grundlage dieser Masterarbeit ist die Erforschung und Optimierung von Synthesen möglicher Duftstoffe. Das Projekt entstand aus einer Zusammenarbeit der Hochschule Merseburg in Merseburg mit dem Unternehmen Miltitz Aromatics GmbH in Bitterfeld-Wolfen (Deutschland).

Duftverbindungen können auf unterschiedliche Weise und mit verschiedenen Methoden synthesiert werden. In dieser Forschungsarbeit wurden Methoden - wie Phasentransferkatalyse und Cope-Umlagerung - erforscht und angewandt, mit dem Ziel, eine hohe Ausbeute und Menge der gewünschten Substanzen zu erhalten, und das ohne Nebenprodukte und irgendwelchen Nebenreaktionen. Dies bezieht die Untersuchung von Synthesen mit verschiedenen Prozessparametern wie Temperatur, Lösungsmittel, Druck und Reaktionszeiten ein. Der Schwerpunkt lag bei den Untersuchungen zur Cope-Umlagerung, eine übliche Methode bei der Synthesierung von neuen potentiellen Duftstoffen. Die Substanzen, die in dieser Arbeit synthesiert wurden, besitzen eine Hepta-1,5-dien-Struktur, die es ermöglicht, in einfacher Weise [3,3]-sigmatrope Umlagerungen, wie Cope-Umlagerung, zu durchlaufen.

Die Basisverbindung aller Untersuchungen war 2,5-Dimethyl-2-vinyl-4-hexenenitril (Neronil). Neronil wird durch eine Alkylierung von 2-Methyl-3-butenenitril mit Prenylchlorid unter basischen Bedingungen in einem Phasentransfer-System synthesiert. Mit dieser Methode konnte isoliertes Neronil mit einer Ausbeute von 35% bis 46% hergestellt werden, in Abhängigkeit von den Voraussetzungen und der Durchführung von Reaktionen. Zusätzlich konnte die Menge von Nebenprodukten verringert werden. Dieses synthesierte Hexenenitril enthält die bereits erwähnte 1,5-Dien-Struktur sowie eine Cyanogruppe, welche eine geeignete Basis für die Synthesierung von neuen potenziellen Duftstoffen darstellt.

Es wurde festgestellt, dass Neronil durch eine Hydrolyse unter basischen Bedingungen in 2,5-Dimethyl-2-vinyl-4-hexensäure transferiert werden kann. Nach fünf Stunden wurde die Säure mit einer Ausbeute von 96% erhalten. Durch die anschließende Veresterung mit Isobutanol konnte der 2,5-Dimethyl-2-vinyl-4-hexensäureisobutylester in einer quantitativen Umsetzung erhalten werden. Die Untersuchungen ergaben, dass Neronil sowie der zugehörige Ester mit 30% beziehungsweise mit 80% Umwandlung in das entsprechende Cope-Produkt umgewandelt werden. Eine Umlagerung der Hexensäure in ein entsprechendes Cope-Produkt konnte nicht beobachtet werden. Die Säure wurde durch das Erhitzen decarboxyliert.

Zur qualitativen Ermittlung von Reaktionslauf und Struktur, wurden Analysen mit GC-MS, ^{1}H-NMR und ^{13}C- NMR durchgeführt.

Stichworte: Duftstoffe, Phasentransferkatalyse, Hydrolyse, Veresterung, Cope-Umlagerung

Resumo

O objectivo desta tese é a otimização e síntese de potenciais fragrâncias. Este trabalho é destinado a um projeto entre a University of Applied Sciences em Merseburg e a empresa Miltitz Aromatics GmbH em Bitterfeld-Wolfen (Alemanha).

Compostos aromáticos podem ser sintetizados de diferentes maneiras e por vários métodos. Neste trabalho, métodos como catálise de transferência de fase e rearranjo de Cope foram investigados e aplicados de modo a obter rendimentos e quantidades elevadas dos compostos desejados e, de preferência, sem produtos secundários e novas reações. Este trabalho envolve o estudo de sínteses com base em diferentes parâmetros de modo a alcançar uma alta qualidade e quantidade de produto, tais como: temperatura, solvente, pressão e tempo de reação. O maior foco foi no rearranjo de Cope, o qual é um método comum para sintetizar novas fragrâncias. Os compostos sintetizados neste trabalho têm uma estrutura hepta-1,5-dieno e por esta razão podem ser facilmente transformados por um rearranjo [3,3]-sigma tropic.

O composto base de todas as investigações neste trabalho é 2,5-dimethyl-2-vinyl-4-hexenenitrile (Neronil). Neronil é sintetizado por uma alquilação de 2-methyl-3-butenenitrile com prenylchloride em condições básicas num sistema de catálise de transferência. Neste trabalho o rendimento de Neronil isolado aumentou de 35% para 46% ao variar alguns parâmetros durante a reação. Adicionalmente a quantidade de produtos secundários diminuiu. Graças à existência de um grupo ciano e à já mencionada estrutura 1,5-dieno, este composto torna possível sintetizar novos potenciais produtos aromáticos a partir dele.

Foi investigado que Neronil pode ser transformado em 2,5-dimethyl-2-vinyl-4-hexenoic acid por uma hidrólise em condições básicas. Após cinco horas o ácido pode ser obtido com um rendimento de 96%. Seguido de uma esterificação com isobutanol para produzir 2,5-dimethyl-2-vinyl-4-hexenoic acid isobutyl ester com uma conversão total. Foi observado que Neronil e o correspondente éster podem ser convertidos nos respetivos Cope-produtos com uma conversão de 30% e 80%. Ao aquecer o ácido de modo a implementar o rearranjo de Cope, um produto de descarboxilação inesperado é produzido.

De modo a seguir o progresso das reações e para confirmar os novos produtos foram realizadas análises com o GC-MS, ^{1}H-NMR e ^{13}C- NMR.

Palavras-chave: Fragrância, Catálise de transferência de fase, Hidrólise, Esterificação, Rearranjo de Cope

List of Abbreviations

bp	Boiling Point
d	Doublet
dd	Doublet of Doublets
EI	Electron Impact
FID	Flame Ionisation Detector
FCC	Flash Column Chromatography
GC	Gas Chromatography
HoMe	Hochschule Merseburg
I	Spin
MA	Miltitz Aromatics GmbH
MSD	Mass Selective Detector
MS	Mass Spectrometry
(m/z)	Mass-to-charge ratio
m	Multiplet
NMR	Nuclear Magnetic Resonance
PTC	Phase Transfer Catalyst/Catalysis
PTFE	Polytetrafluoroethylene
R_f	Retention factor
RT	Retention time
s	Single
S_N2	Nucleophilic Substitution
TBAB	Tetrabutylammonium bromide
TLC	Thin Layer Chromatography
TEBAC	Triethylbenzylammonium chloride
t	Triplet
2M3BN	2-methyl-3-butenenitrile

List of Units and Symbols

σ	Sigma
cm	Centimeters
eV	Electron Volts
h	Hours
K	Kelvin
MHz	MegaHertz
m	Meter
µL	Microlitre
µm	Micrometre
mbar	Millibar
mL	Millilitre
min	Minutes
nm	Nanometre
ppm	Parts per million
π	Pi
pA	Pico Ampere
s	Second
^{o}C	Degree Celsius
%	Percentage

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1. Introduction and Objectives

Fragrances are mixtures of aromatic compounds, essential oils and solvents. They give a pleasant odour to rooms, objects or living bodies (human or animal). Perfumes are used since ancient times and the industry of cosmetics is increasing each year. Synthetic fragrances may be more expensive to produce than natural aromatic ones, but they are more consistent and have a higher durability. Producers intend constantly to create new aromas and to improve the existing flavours. Some perfumes can cause health or environmental problems when used in excessive quantity or due to the impurities of the substances. The most common effects on people are allergy, asthma but also cancer, usually not due to their main chemical compound, but based on secondary components [1], [2].

The goal of this project is to synthesize new flavours by technical optimization of reaction procedures, while research in literature and practical experiments are taking place. Different parameters and conditions are tried out in the executed procedures, like solvent, raw materials, temperature, pressure and reaction time in order to study the behaviour of the reactions and achieve high quality and quantity of the products. For an efficient characterization of new products, it is necessary to develop analytical and purification methods.

All the products are developed from 2,5-dimethyl-2-vinyl-4-hexenenitrile, allowing to be the base material in this work. This substance is interesting to study because of its cyano group and his 1,5-diene structure. The cyano group of this compound can be converted into an acid or ester. The 1,5-diene structure can undergo to a sigma tropic rearrangement like Cope-Rearrangement from which it is known that these flavoured compounds can arise from. The target compounds have a hepta-1,5-dienestructure which allows to implement a Cope-rearrangement to the compounds in this work and therefore to transform them into a hepta-2,6-dienestructure.

Miltitz Aromatics (MA) is an independent German company located in Bitterfeld-Wolfen near Leipzig. Miltitz produces fragrances and flavours based on synthesis of chemical products. The company is selling all over the world and is well known for supervising and improving the quality of its products through research and new developments [3]. On this basis, MA started a joint cooperation with the Organic and Macromolecular Chemistry Lab of the Hochschule Merseburg (HoMe) – University of Applied Sciences – under the supervision and orientation of Prof. Thomas Rödel [4].

2. Literature review

All target syntheses to investigate in this thesis are illustrated in *Figure 1*. The basic substance is 2,5-dimethyl-2-vinyl-4-hexenenitrile, also called Neronil (in bold). This compound is synthesised by an alkylation of 2-methyl-3-butenenitrile with prenylchloride. Neronil is a very capable compound because of its 1,5-diene structure. This unsaturated configuration is known for a good reactant in sigmatropic rearrangements. Based on the cyano group, new functional groups can be introduced into the molecule. The 2,5-dimethyl-2-vinyl-4-hexenoic acid is formed by a basic hydrolysis from Neronil. From this acid an esterification can be performed to get 2,5-dimethyl-2-vinyl-4-hexenoic acid isobutyl ester. Another attempt is to form this product directly via acidic hydrolysis in the presence of an alcohol from the Neronil. To conclude the Cope-rearrangement of these compounds is performed: nitrile, acid and ester.

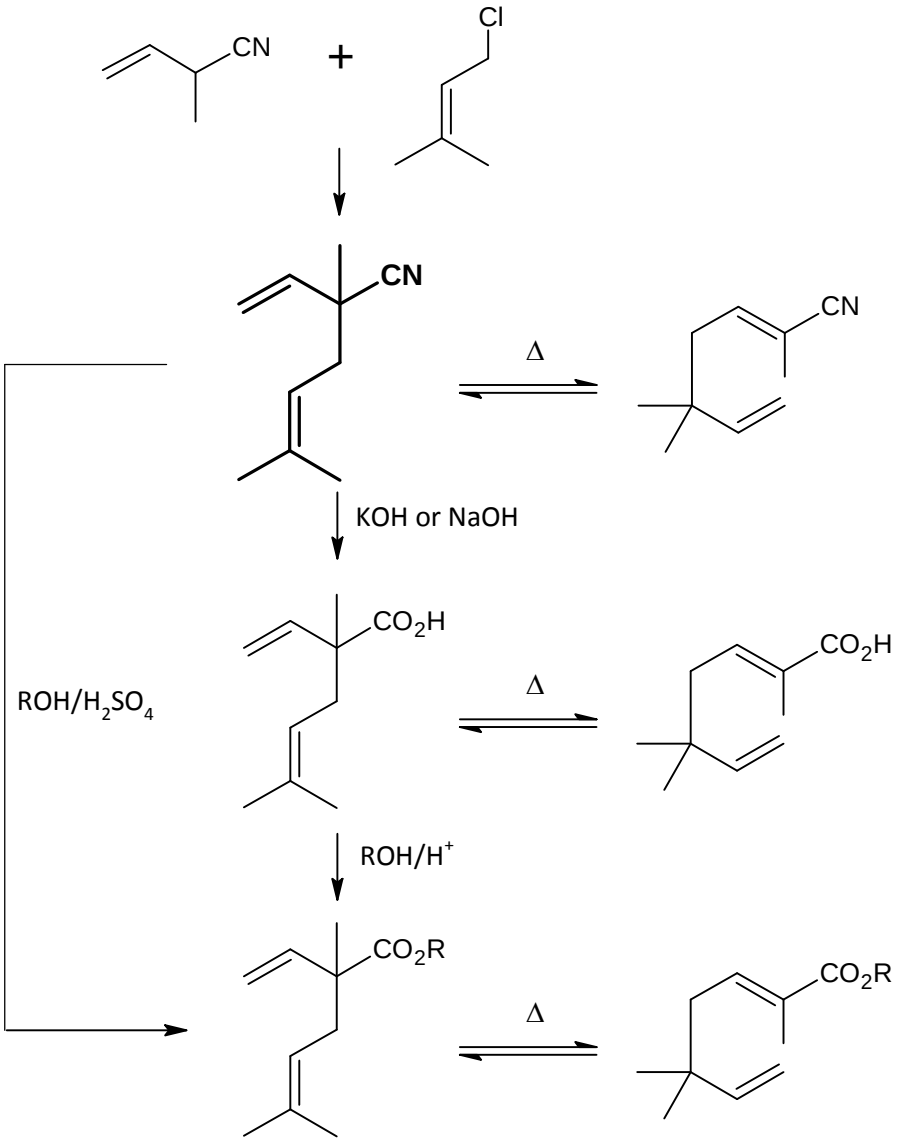


Figure 1: Scheme for planned synthesis

2.1. Synthesis of the Neronil

The colourless compound 2,5-dimethyl-2-vinyl-4-hexenenitrile **3** has a soft, sweet and fruity aroma and is named Neronil. The optimization of the synthesis for this product has already been researched in previous work [5].

Neronil is produced by alkylation of 2-methyl-3-butenenitrile **1** with 1-chloro-3-methyl-2-butene **2** under phase transfer catalysis (PTC) conditions. The reaction is illustrated in *Figure 2*. The alkylation takes place via an S_N2-mechanism, which means bond building and bond breaking passes synchronously.

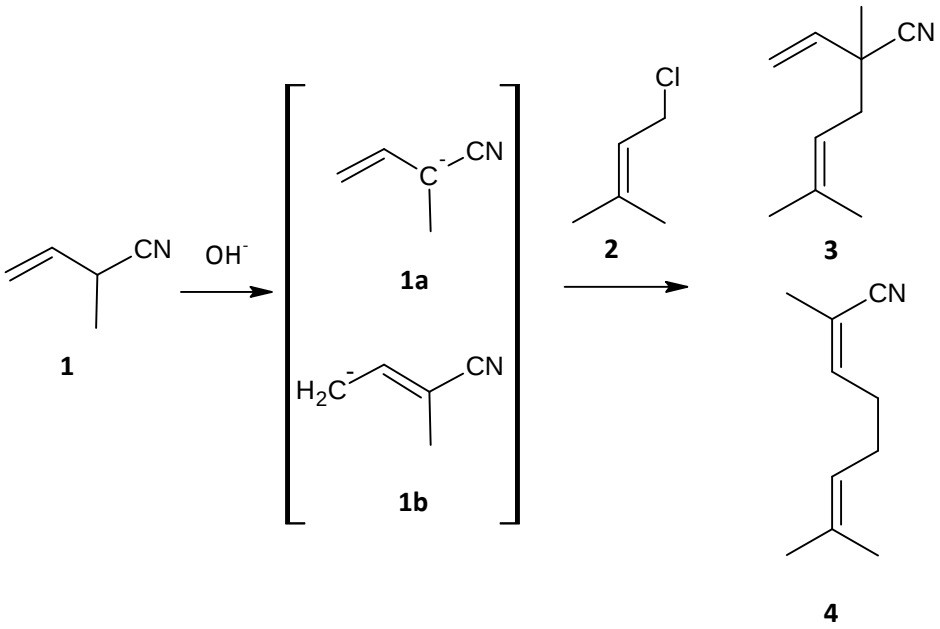


Figure 2: Alkylation of 2-methyl-3-butenenitrile with prenylchloride

In the first step of the synthesis, the 2-methyl-3-butenenitrile **1** is deprotonated at the α-position using alkali hydroxides and as a result a tertiary carbanion **1a** is formed, a good nucleophile for the S_N2 reaction. This anion is rearranged to structure **1b** by resonance effect where the electron pair from the tertiary carbanion is moved to the primary carbon atom and the double bond is shifted to the β-position. The prenylchloride **2** can be attacked from either carbanion **1a** or **1b** and as a result two products can be formed: the main product 2,5-dimethyl-2-vinyl-4-hexenenitrile **3** and the side product 2,7-dimethylocta-2,6-dienenitrile **4**.

Steric hindrance can cause a problem preventing S_N2 reactions to occur. The bigger the congestion around the vicinity of the leaving group, the slower the reaction will proceed [6], [7]. For this reason, prenylchloride as a primary alkyl chloride can be easily attacked by the anion of **1.**

2.1.1. Phase Transfer Catalysis

Phase transfer catalysis (PTC) is a special heterogeneous catalysis and has been widely explored for five decades in syntheses of organic compounds. The purpose of using PTC is to facilitate the migration of the reactant from two immiscible phases in a reaction. The utilisation of phase transfer catalysis in reactions provides lower reaction times and temperatures, less side products and higher conversion and yields. Also a unique advantage of this type of catalysis is the dispensing of the requirement to use expensive solvents that dissolve all reactants in one phase. The most common phase transfer catalysts are quaternary ammonium and phosphonium salts [8].

An overview of the mechanism of PTC of nucleophilic substitution is illustrated in *Figure 3*. The catalyst moves forth and back from organic phase to the aqueous phase [9]. In the beginning, the quaternary ammonium halide (Q^+X^-) dissolves in the aqueous phase where the anion (X^-) undergoes an exchange with the anion (Y^-) from reactant dissolved in the aqueous phase. The ion-pair formed (Q^+Y^-) travels to the organic phase, this step is called phase transfer. There, the anion (Y^-) undergoes a nucleophilic substitution in a reaction with the organic reactant and the final product (RY) is formed. The catalyst (Q^+X^-) returns to the aqueous phase, where the cation (Q^+) can bound with the new anion (Y^-) and the same cycle of the ion-pair reinitiates [10].

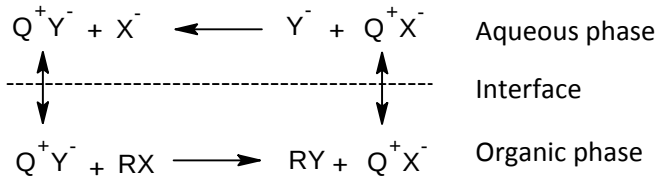


Figure 3: PTC reaction mechanism

In the previous work [5] conditions for preparing Neronil under PTC were developed. In the alkylation of the 2M3BN with prenylchloride, sodium or potassium hydroxide is used as base. This reaction is not possible without the presence of the PTC, because the reactants are located in two immiscible phases. As *Figure 4* shows, the base is located in the aqueous phase and the 2M3BN in the organic phase [11], [12]. In [5] two catalysts were used: tetrabutylammonium bromide (TBAB) and triethylbenzylammonium chloride (TEBAC).

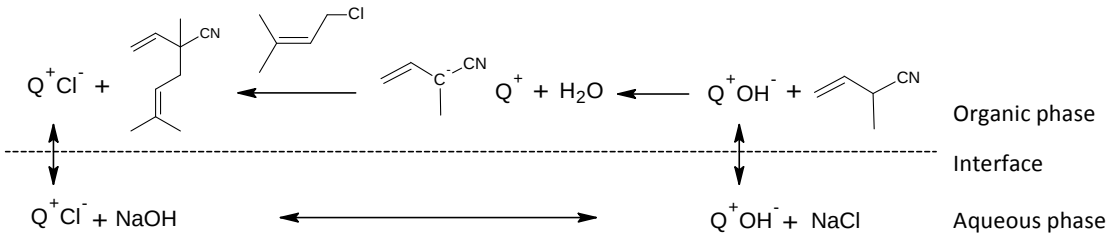


Figure 4: Alkylation of 2M3BN with prenylchloride under PTC conditions

When the catalyst is added to the reaction it is submitted to an anion exchange with the bases in the aqueous phase. As a result Sodium Chloride (NaCl) is formed and stays in this phase, while the quaternary ammonium hydroxide (Q^+OH^-) travels to the organic phase. The transferred ion-pair reacts with the 2M3BN by deprotonation of the α-position of the nitrile - as explained before. Then the alkylation of the carbanion with prenylchloride occurs and the final product Neronil is formed. The quaternary ammonium chloride migrates to the water phase and the cycle continues [13].

2.1.2. Previous studies of Neronil synthesis

In the previous work [5] a Neronil synthesis was developed by studying the influence of changing parameters like solvent, catalyst, base, concentration ratio of starting material and reaction temperature. It was found, that the most successful procedure consists in a reaction system with 2-methyl-3-butenenitrile and prenylchloride with an equivalent of 1:1.3, KOH powder as base and TBAB as phase transfer catalyst in cyclohexane as solvent. With these conditions a conversion of 100% of the starting material is reached in only one hour with a maximum yield of 40%, although the most common yield obtained from this synthesis has an average of 35%.

During the synthesis of Neronil two side products are formed and the choice of parameters of this procedure has already been taken in consideration. Using sodium hydroxide as base produces less side products, on the other hand the reaction is much slower. In case of using potassium hydroxide, a higher yield is obtained.

The amount of this first side product rises during the performance of the reaction and in particular when the base is aqueous. The product is identified as bis(3-methylbut-2-en-1yl) ether **5** and has a similar retention time as Neronil. That is why the separation from Neronil during the purification is not possible. This leads to one of the objectives of this project: to reduce the amount of ether from the reaction. In [5] it was verified that at first a hydrolysis of the prenylchloride occurs where 3-methyl-2-buten-1-ol (prenol) **2a** is formed. The alcohol is deprotonated by a hydroxide ion - as illustrated in *Figure 5*. Next, a nucleophilic substitution of the alkoxide **2b** at prenylchloride **2** takes place, in order to yield ether **5**.

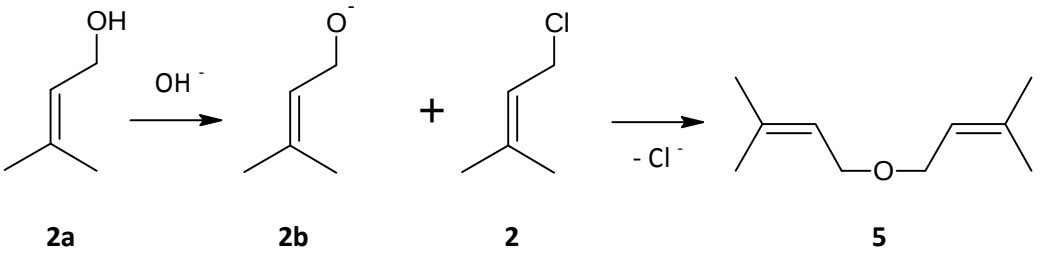


Figure 5: Synthesis of side product bis(3-methylbut-2-en-1yl) ether

A further problem during the alkylation of 2M3BN with prenylchloride under PTC conditions is a strong exothermic reaction that occurs after a while when adding the raw materials to the KOH powder. Also a second side product is formed. In case of using KOH powder as base, the amount of the product 2,7-dimethylocta-2,6-dienenitrile **4** increases - illustrated in *Figure 2*. This side product **4** is thermodynamically more stable than the Neronil because of the double bound in conjugation with the cyano group and for that reason by increasing the temperature of the reaction this compound is produced. On the other hand, it is not detected in GC-MS and therefore assumed that it is first deprotonated by a hydroxide anion and then alkylated again with prenylchloride **2** - as illustrated in *Figure 6*. The reaction product is identified as 2,7-dimethyl-2-(3-methylbut-2-en-1-yl-)-octa-3,6-dienenitrile **6,** remaining in the residue with more than 80% after the distillation of the reaction mixture.

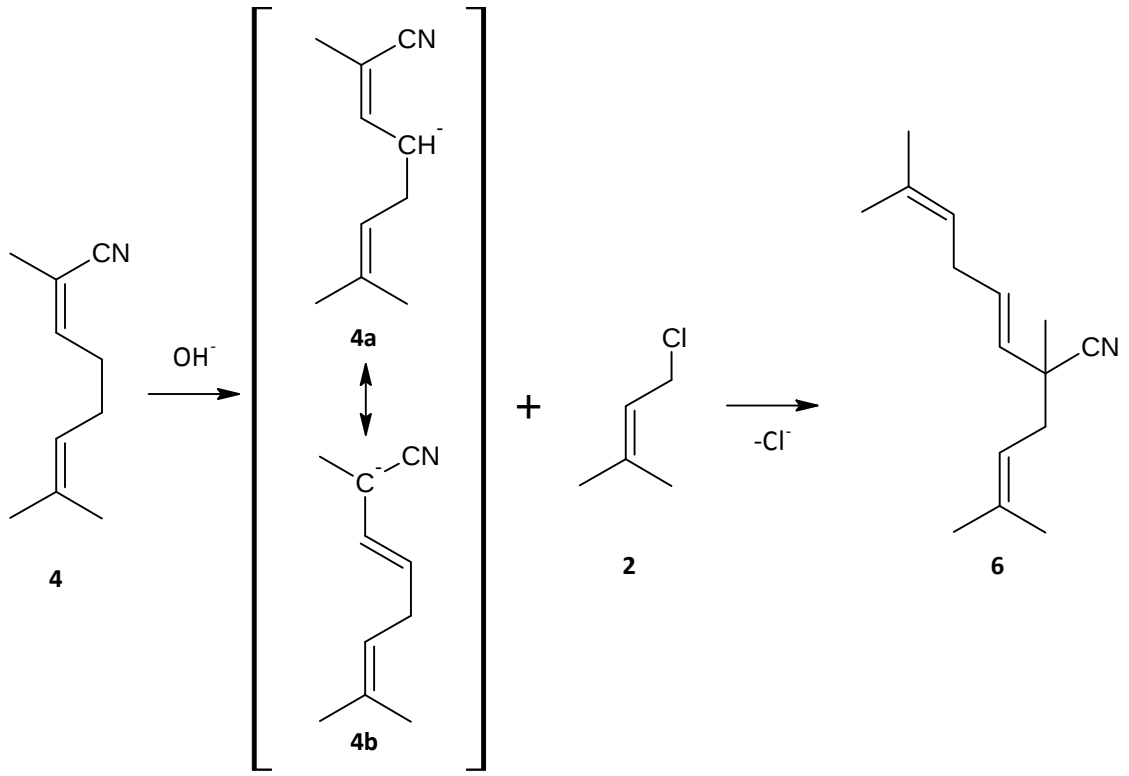


Figure 6: Synthesis 2,7-dimethyl-2-(3-methylbut-2-en-1-yl-)-octa-3,6-dienenitrile

2.2. Hydrolysis

Hydrolysis is an addition of water on a positive polarised atom and can be catalysed by bases or acids. Under normal conditions only few organic compounds react easily with water. Hydrolysis very often involves a catalyst, heat steam and pressure. The catalyst is added in order to speed up the reaction and to conclude the hydrolysis when water has no effect.

In the hydrolysis of the cyanide group, a carboxylic amide is formed as an intermediate product and at the end it leads to the carboxylic acid. The hydrolyses under acid and basic conditions performed in this work to produce 2,5-dimethyl-2-vinyl-4-hexenoic acid **7** are described in *Figure 7.* The reaction does not stop when the amide is produced because the rate of hydrolysis of amide is bigger than the one of the nitrile. Since the nitrile group is not very reactive, the use of bases at high temperatures or the use of strong acids is required [14]. When hydrolysing under basic conditions, it is common to use sodium or potassium hydroxide solutions. When performing hydrolysis under acidic conditions, it is possible to use: concentrated hydrochloride acid, 25% to 75% aqueous solution of sulfuric acid or concentrated phosphoric acid [15].

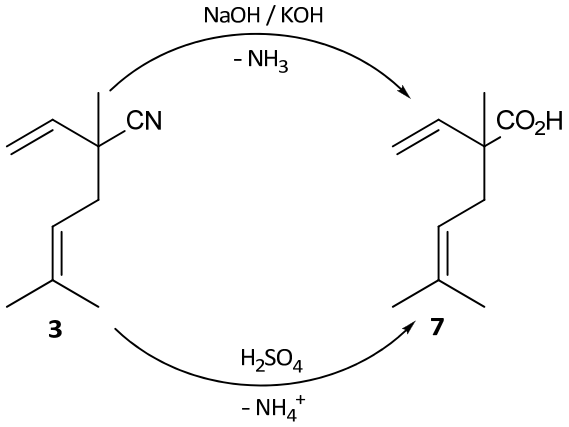


Figure 7: Hydrolysis of the Neronil under or basic conditions

Hydrolysis of nitriles under basic conditions can have yields around 90%. Prout and his co-workers found that saturated carboxylic acids (like 3-benzyl-methyl-pentane acid) are formed in a yield of 91%-93% when the nitrile is treated with potassium hydroxide and glycol under reflux for six hours [16]. More specifically, for an unsaturated carboxylic acid like (3-carboxypyridine) a yield of 90% is obtained when hydrolysis is performed with sodium hydroxide in ethanol by refluxing the mixture for three hours [17].

Experiments of hydrolysis of unsaturated nitriles under acidic conditions achieve yields between 60% and 90%. For example, a yield of 63% is obtained for 1-naphthaleneacetic acid

by using hydrochloric acid for the hydrolysis. By refluxing an aromatic unsaturated nitrile like (2,4,6-trimethylcyclohexane-cyanomethide) for five hours in the presence of a 40% aqueous solution of sulfuric acid a yield of 87% is carried out [18], [19]. In his work Starks determined, that after one hour under acid conditions approximately 50% of a long branched chain nitriles had been hydrolysed to the acid [20].

2.3. Esterification

The esterification is a replacement of the hydrogen of the COOH-group by a type of hydrocarbon group. The most simple and common way to synthesise the ester is a direct esterification of the carboxylic acid with an alcohol and an acidic catalyst - this type of reaction is called Fisher Esterification. A very common catalyst for this reaction is sulfuric acid, but other catalysts are used too, like p-toluolsulfonic acid or naphthalenesulfonic acid [21]. The synthesis of an ester is a reversible reaction, that is why it is possible to shift the balance to the product side by an excess of the reagents or one of the products has to be removed during the reaction. In general the water formed during the reaction has to be retrieved [22].

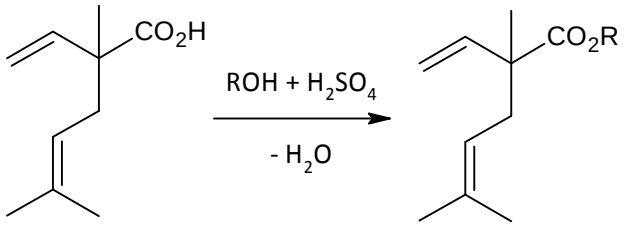


Figure 8: Esterification of the acid

The general reaction of the Fisher Esterification of the acid **7** is summarised in *Figure 8* - different alcohols can be used. Leconte and Denis found that the esterification of carboxylic acid like (methylglutaric acid) with methanol takes six hours under reflux and as a result a yield of 93% is reached with a purity of 99% of ester. The conversion of the carboxylic acid in this synthesis is 95% [23].

2.4. Cope-rearrangement

2.4.1. The principle

The Cope-rearrangement is an organic reaction that converts a 1,5-diene structure to another 1,5-diene isomer structure by thermal treatment. This reaction is named after the chemist Arthur Clay Cope. It is a concerted process where at the same time, bonds are broken and formed in order to change their position but not their structure. It is an equilibrium

reaction where the thermodynamically most stable isomer is the main product [24]. It has been proven that Cope-rearrangements are useful in the synthesis of fragrance and flavour compounds as in laboratory or in industrial scale [25].

The reaction is assorted as [3,3]-sigma tropic rearrangement, which is integrated to a class of pericyclic reactions. In the 1,5-diene structures there is a bi-allylic bond, this bond is relatively weak and therefore easy to cleave. The numbering [3,3] means that three carbon atoms separate the site where the σ-bond is broken from the one that is formed. This numbering is unrelated to the nomenclature of the molecule, designated as such only for a better understanding of the mechanisms of the rearrangement. During the rearrangement a transition state is achieved, where the allylic σ-bond and one of the π-bonds are already broken and the new σ- and π-bonds partially formed - represented in *Figure 9* as dashed lines. The transition state corresponds energetically and structurally to two allylic fragments. At this moment these radicals have a perfect orbital symmetry and while interacting with each other the new carbon bonds are formed. The high energy applied to the reaction is required for the migration of the three electrons in this state. The transition state is only a tool to clarify the radical process in the cyclic geometry [26], [27].

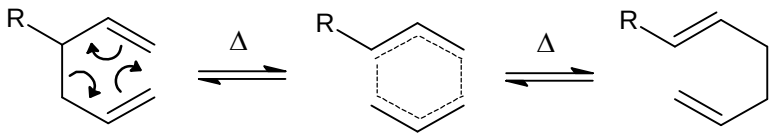


Figure 9: [3,3]-Sigma tropic rearrangement

The performance of these reactions has been intensively studied for several decades. In the case of purely thermal rearrangements, most of them need a range of temperature from 150 °C up to 350 °C, depending on the structure and substitution of the compound [25]. But a typical range from 150°C to 200°C can be defined for aliphatic substances including unsaturated, activating substituents like phenyl, cyano or carboxyl groups. With the presence of additional activating groups in the compound, the reaction temperature reduces more [27]. However, a far greater proportion in the studies of Cope-reactions deals with catalytic rearrangements. By using catalysts, like Palladium dichloride, the temperatures for rearrangements decrease until room temperatures [28]. It has been proven by Wigfield and Feiner that the polarity of the solvents has no influence on the Cope-rearrangement [29].

In this work, the investigations of Cope-rearrangement were limited to thermal rearrangements, because the common catalysts for Cope are very expensive in the case of industrial use. Therefore several solvents with different boiling points were used to study the relation of reaction pressure.

The common procedure is to seal the raw material in a closed reaction vessel, pure or dissolved in a solvent, and to heat it in an oven [30] or a hot bath of water or silicone oil [29], providing a higher pressure to the reaction. Alternatively, a mixture of raw material and solvent is refluxed without any pressure [31]. In Cope-rearrangement investigations it is common to add the solvent with an equivalent of 1:10 to the raw-material [32], [33].

2.4.2. Cope-rearrangement of Neronil and its analogues

The structure of Neronil, the corresponding acid and ester offer the characteristic 1,5-diene structure, which provides the condition to perform a [3,3]-sigma tropic rearrangement - as illustrated in *Figure 10*.

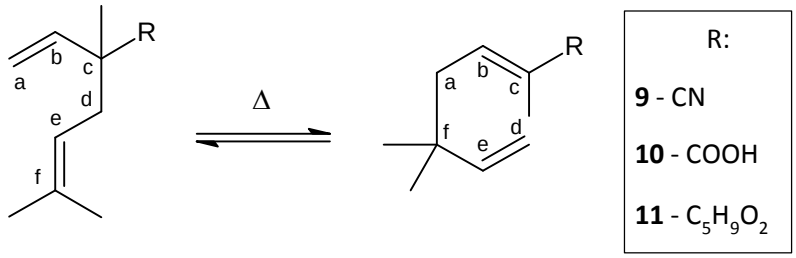


Figure 10: Mechanism of Cope-rearrangement of Neronil and its analogues

The starting compounds for Cope-rearrangements have all the same 2,5-dimethyl-2-vinyl-4-hexene structure. During transformation the σ-bond (C_c-C_d) in the reactant is broken and a new σ-bond (C_a-C_f) in the product is formed.

During this process, the π-bond (C_a-C_b) attacks the carbon atom f, forming a new σ-bond in that position, thereby the π-bond (C_e-C_f) is displaced between the positions e and d. While the σ-bond (C_c-C_d) is broken, a new π-bond between positions c and b is formed.

Successful rearrangements in this research lead to the products 2,5,5 –trimethyl-2,6-heptadienenitrile **9**, 2,5,5-trimethyl-2,6-heptadienoic acid **10** and 2,5,5-trimethyl-2,6-heptadienoic acid isobutyl ester **11.**

2.5. Analytical Methods

All reactions during the practical work are followed by analytical methods. In all cases previous separations and purifications of the products need to be performed. The purpose of analytical techniques is to separate, identify and quantify the chemical components of the reaction. An analytical method used is Gas Chromatography – Mass Spectrometry. A complementary instrumental method used to confirm new products is the Nuclear Magnetic Resonance.

2.5.1. Gas Chromatography – Mass Spectrometry

As the name suggests, this instrumental technique combines Gas Chromatography and Mass Spectrometry. Using both units together, instead of individually, allows you to have a more efficient analysis [34]. GC-MS is used to separate chemicals mixtures, identify unknown products and quantify known substances.

The Gas Chromatography (GC) separates all compounds in a sample by transporting them through a polymer coated column. The division is based on the different chemical properties of each molecule, such as volatility, shape, weight and affinity for the stationary phase of the column. Compounds with a higher volatility and a lower mass are separated first [35].

The function of the Mass Spectrometry (MS) is to identify the separated compounds. The eluted substances enter into the ionisation source where they are blasted with electrons and converted into positively charged particles. These ions are then separated based on their mass, by passing through an electric or a magnetic field. Ions with the same mass-to-charge (m/z) ratio will suffer the same amount of deflection. In the end the instrument measures the charge, displaying the results in a spectrum according to the number of ions detected and their respective mass.

The individual molecules of the sample can be identified comparing their mass spectrum to the known mass spectra of a database.

Another common detector used is a Flame Ionisation Detector (FID). The sample is introduced into a hydrogen flame where the organic compounds will combust and form ions which are then detected by the FID [36].

2.5.2. Nuclear Magnetic Resonance

The nuclear magnetic resonance spectroscopy is used to study the structure of molecules by immersing the nuclei of the atoms in a magnetic field where they absorb and re-emit electromagnetic radiation. The nuclei of many isotopes have an intrinsic magnetic moment and angular momentum, which is called spin (I). All these nuclei in NMR (^{1}H , ^{13}C, ^{19}F or ^{31}P) have a half-integer spin, although the first two are more common in research. In the presence of an external magnetic field the spins are aligned and their magnetic moment flips. When removing the external field the nucleus returns to its original state, called relaxation. During this process the nucleus emits electromagnetic radiation and these signals are received by the spectrometer. A reference signal from a standard compound is added to the sample. This compound is chemically unreactive, easy to remove after the measurement and is usually tetramethylsilane ($(CH_3)_4Si$) [37].

This technique is complementary to other structural and analytical techniques when studying organic compounds. The advantage of NMR is the ability to be a non-destructive,

quantitative study of molecules in a solution and in solid state as well as the possibility that the samples can weigh less than a milligram [38] [39].

2.6. Purification Methods

After a reaction, purification methods have to be executed. The desired substances can be extracted from the obtained product mixture by carrying out techniques, such as: distillation, recrystallisation or chromatography. The of separating the chemical mixtures is to isolate the target product in order to analyse the substance with the analytical methods explained to get characteristic properties of the compound and to calculate the yield of the reaction, although the main reason is to obtain a pure compound [40].

2.6.1 Distillation

Distillation is one of the most common separation techniques for a liquid mixture by heating it up. It is a physical separation by selective evaporation and condensation, being the most volatile liquid evaporated first. This vapour will condense when passing throw the condensing column. Simple distillations are performed when the liquid is only less than 10% impure or has a non-volatile component or even when the difference between the boiling points (bp) of the liquids is more than 70 ^{o}C. It is also possible to check the boiling point of a substance. When the boiling points of the components are too similar a fractional distillation is performed, providing theoretical plates. A theoretical plate in a rectification column stands for one simple distillation, being equivalent to one vaporisation-condensation cycle. The more theoretical plates are added, the more efficient the distillation becomes, but it will take longer and more energy is required to keep re-evaporating the liquid and condensing the gas. Another technique is the vacuum distillation when the bp of the component is too high. The vacuum is provided by a mechanical pump that will reduce the pressure while substances are distilled at a lower bp [41], [42].

2.6.2. Chromatography

This technique allows a mixture to be distributed over two immiscible phases and separated into the individual components. The sample is dissolved in a mobile phase, which can be liquid or gaseous. The mobile phase flows with the solved components through the immobile phase. The different components travel at different rates in the stationary phase causing them to separate. The phases are chosen to provide the compounds in the sample with a different solubility. As a result, substances with more affinity in the stationary phase take longer to travel through than a more soluble component in the mobile phase. These techniques are used in this practical work, such as Thin Layer Chromatography (TLC), Flash Column Chromatography (FCC) and Gas Chromatography (GC) - as mentioned in chapter 2.5.1. [43].

In the Thin Layer Chromatography, the stationary phase is a thin uniform layer of silica gel on a glass or rigid plastic plate. On these plates small drops of the solution mixture are placed, and then the plates are placed in a covered glass tank with a solvent in order to be saturated in the atmosphere. The solvent travels slowly up the plate taking the components along, separating them. The migration of an analyte through the stationary phase can be calculated, dividing the distance travelled of the compound on the plate by the distance travelled of the solvent. The quotient is called retention factor (R_f).

If the compounds are not visible for identification, a UV lamp can be used to illuminate the plate. The plates contain a fluorescent dye, which will glow under UV light, except where the spots of the organic compound are placed [44].

The Flash Column Chromatography works as TLC although in a bigger scale by packing a solid adsorbent as a stationary phase in a vertical column. The sample is added to the column, next a liquid solvent as mobile phase is added on top, flowing down the column by gravity or pressure. As the eluent travels through the stationary phase and takes the components along, the elutants are separated. The elution of the less polar substances goes faster because of its low affinity to the solvent and the silica gel. The more polar components adsorb more the stationary phase and they travel more slowly through the column. When the separation has already been performed but the second component was not collected, a more polar solvent eluent can be used during the elution. This eluent will compete for space with the polar substances in the stationary phase, so they are not able to stick to it any longer and need to move along the column.

It is common that the compounds - needed to be isolated in FCC - are colourless like purification of organic compounds. In these cases the eluent is collected sequentially in different tubes and then analysed [45].

The adsorbents used as stationary phase are usually silica gel or oven alumina, which is used more in FCC than in TLC. A good choice of the solvent guaranties an effective separation of the compounds. If the eluent is very polar the separation will not occur. The movement of the mixture will be too fast and if the eluent is not polar enough, the components of the mixture will not elute from the column [46].

3. Results and Discussion

3.1. Synthesis of the Neronil

Before the optimization of the synthesis of 2,5-dimethyl-2-vinyl-4-hexenenitrile **3**, some experiments with the known procedure of the previous work [5] are tried out to observe the reaction performance.

Instructions for this synthesis are: adding in a flask at first the phase-transfer catalyst TBAB, the base KOH as a powder and the solvent cyclohexane; then 2-methyl-3-butenenitrile and prenylchloride are consecutively added drop wise to the mixture and the reaction is performed for several hours with a temperature of 60 ^{o}C. The progress of the reaction is followed by a GC-MS analysis. Using this procedure experiment 1 and 2 are performed, while in the second case the base is changed to NaOH in order to investigate the variation of formed side products.

These experiments prove that the reaction is reproducible, but a yield with an average of only 30% was achieved, therefore primary mistakes in these reactions need to be taken into account. As in the previous work it is also confirmed that the reaction takes longer when sodium hydroxide is used as base, also less ether is produced when using potassium hydroxide. Nevertheless, the biggest problem of this procedure is a strong exothermic and uncontrollable reaction that occurs when using potassium hydroxide. Additionally, when heating up the reaction to over 60 ^{o}C for a longer period of time the base gets stuck in the flask and stirring the two phases is not possible anymore, reason why the reaction is terminated.

With the objective to decrease the amount of side products, to control the temperature and with that to improve the yield of the reaction, the execution of procedure I is modified.

Procedure II is implemented with the same raw-materials as used before, although in a different order. First cyclohexane, TBAB, 2M3BN and prenylchloride are mixed together at room temperature; then the reaction mixture is heated up to 60 ^{o}C and finally the base is added in small quantities during the reaction. With this procedure the problem of the strong exothermic reaction that has been mentioned before was solved. The reaction temperature stays stable until the end of the experiment, but during the procedure, the basis sticks to the flask and to the stirrer.

One explanation for this fact is because of the formation of water during the reaction. To avoid this situation, a new procedure is applied where the water is removed from the reaction mixture. In procedure III, first TBAB, base and cyclohexane are mixed together and the temperature is raised until the boiling point of the solvent; then a mixture of 2-methyl-3-butenenitrile and prenylchloride (1:1.3) is added drop wise to the flask. During the reaction the water is separated in a Dean-Stark apparatus, to influence the reaction equilibrium and to

decrease the amount of side products. In order to reduce the reaction temperature n-hexane is used as a solvent, but in this case the amount of water separated from the reaction is less. Alternatively the raw-material is dropped very slowly to avoid formation of side products.

Several reactions are performed with these new procedures; an overview of the achieved results is referred in *Table 1*. It is important to mention that the best yield is achieved when using sodium hydroxide as base. In an overall average the yields are between 35% and 46%, resulting in an increase of about 10% compared with the yields achieved in procedure I.

Table 1: Synthesis of Neronil with procedure II and III

Experiment	Procedure	Base	Reaction time (h)	Yield (%)	GC-MS Results (%)		
					Neronil (3)	Ether (5)	Side products
3	II	NaOH	30	46	65	11	24
4	III	NaOH	14	45	67	3	30
5	III	KOH powder	18	35	60	10	30
6	III	NaOH*	8	46	64	0.4	36
7	III	KOH powder*	19	40	60	5	35

*Using as solvent n-hexane

As known from earlier works the amount of the produced ether is less when sodium hydroxide is used. The only exception is experiment 3 carried out with procedure II, where a good yield is achieved. The amount of ether is increased, because the reaction time is longer. On the other hand, the further side products formed with procedure II are the lowest. Comparing all experiments shows that the best performance is experiment 6 using procedure III in which the water is removed during the reaction. With the use of sodium hydroxide as base and n-hexane as solvent, as well as reducing the reaction temperature to 70 ^{o}C, in the end almost no ether has been formed.

The *Figure 11* compares the experiments with Neronil. After isolation of the product a yield up to 46% is achieved. A very important fact is that with the new changes in the procedures the reaction does not have an exothermic moment anymore and gets therefore a better performance. Another significant aspect has been confirmed with these experiments; using sodium hydroxide as base gives an advantage in reducing the amount of side products.

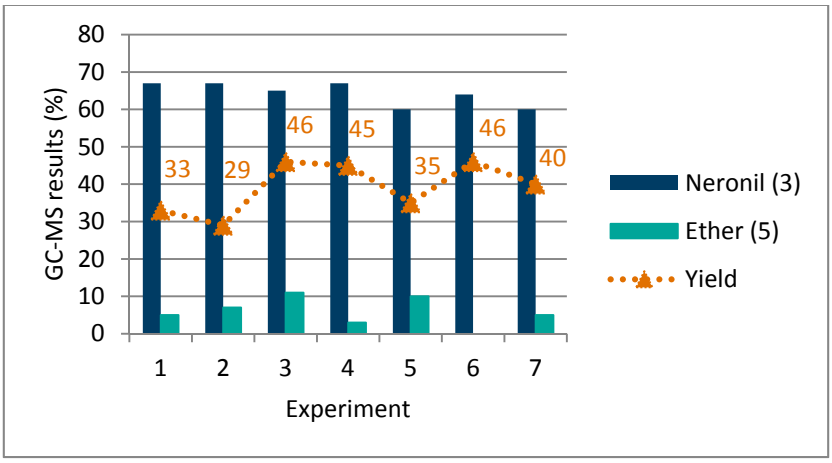


Figure 11: Neronil synthesis results

Important to study in this kind of synthesis is the conversion of the raw-material to the final product during the reaction. In this case experiment 3 serves as an example - illustrated in *Figure 12*. The reaction is stopped when the conversion of prenylchloride is completed at 100%, but the conversion of 2-methyl-3-butenenitrile achieved only 85%. After twelve hours a significant increase of ether is observed. By this time the amount of prenylchloride has decreased much faster than with 2-methyl-3-butenenitrile, proving the reaction mechanisms of the side products with prenylchloride studied in the previous work.

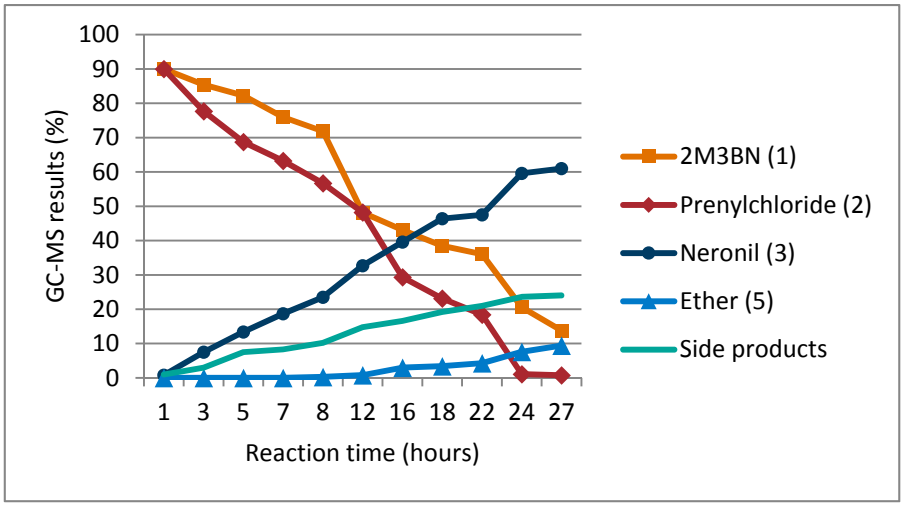


Figure 12: Relation of educts and products during reaction time in experiment 3

Comparing the new results from the synthesis of Neronil with previous works, a better performance of the synthesis is achieved, resolving the problem with the spontaneous exothermic reaction. In order to achieve a perfectly pure product the use of sodium hydroxide as base is implemented. It has been proven that the formation of ether dependents on time, therefore reducing the reaction time allows a higher quality of the product. Overall the yield has risen from 35% to 46%.

3.2. Synthesis of the acid

For the synthesis of the 2,5-dimethyl-2-vinyl-4-hexenoic acid **7** the corresponding nitrile is hydrolysed under basic and acidic conditions.

In a first attempt of the hydrolysis under basic conditions, aqueous sodium hydroxide and Neronil are mixed in a reaction flask and refluxed. It is noticed that two immiscible phases are formed and therefore needed to be stirred very fast. Because of the problem that they don't mix well, the reaction time is extremely long and only a yield of 41% is achieved. The results from these experiments are outlined in the *Figure 13*.

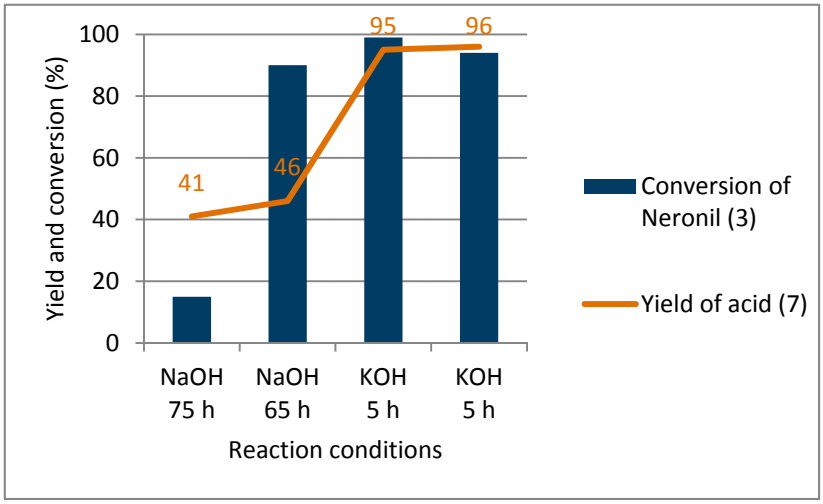


Figure 13: Reaction results of the acid under basic conditions

To avoid this situation and reduce the reaction time, ethylene glycol is added to the reaction mixture as a solubilising solvent in the following experiments. As a result the reaction performance is much more efficient and the conversion of Neronil is achieved earlier, taking more than two days with a yield of less than 50%. To achieve still a greater reduction of the reaction time, a stronger base - in this case potassium hydroxide - is introduced. In experiments using potassium hydroxide in a glycol/water mixture, the conversion of Neronil is always over 90% after only five hours. After isolation and purification by a vacuum distillation a yield of 96% of the acid with a purity of more than 99% is achieved.

This new compound is checked by GC-MS and ^{1}H-NMR analysis and proven to be the target product 2,5-dimethyl-2-vinyl-4-hexenoic acid **7.** Therefore, the best way to synthesise the acid is using potassium hydroxide and a mixture of ethylene glycol and water under heating. a conversion of 95%-99% is achieved when leaving the reaction under reflux for five hours. With the isolation of the acid a yield of 96% is obtained and the acid has a purity of 99%. The fragrance of this acid **7** is different from the Neronil **3**.

Despite of these good results, the synthesis of the acid **7** is carried out also under acidic conditions, as this procedure offers the possibility of a direct esterification of the nitrile in a one-pot-reaction. Using sulfuric acid (96%) and isobutanol is a common procedure in Miltitz Aromatics but never with Neronil, which in this research is tried out. First sulfuric acid and water are heated to 80 °C and then Neronil **3** is dropped into the mixture. Monitoring the reaction progress by GC-MS analysis shows that no acid **7** is formed. Instead, a new main product - besides other side products - is found in GC at nearly the same retention time as the acid, although with another m/z.

Consequently, variations of this procedure have been carried out to reduce the amount of side products. The first experiment is a reduction of the concentration of sulfuric acid to 50% and stirring it with Neronil at room temperature. After one day the conversion of Neronil is accomplished. Rising the reaction temperature up to 50 °C in this system, the conversion of Neronil is much faster, only five hours are needed. The reaction is then heated to 80 °C and as a result the conversion of Neronil is 100% only after four hours. However, in every experiment the side products maintain formed besides the new unknown product, reason why the isolation and purification of this new product is problematically. The separation of the main product cannot be managed with a vacuum distillation. Only 80% purity of the target compound is achieved.

Another separation technique is the Flash Chromatography. To develop optimal conditions a Thin Layer Chromatography is realized. For a good separation of the new product and side products on TLC, the best eluting solvent mixture, cyclohexane and ethyl acetate with an equivalent of 8:1 is developed - as illustrated in *Figure 14*. Comparing the mixture with the acid **7** and the ester **8** proves that a new product has been synthesised. The polarity of the 20% of side products is in between the acid and the ester. The new unknown compound has a high-polar structure. However, a Flash Chromatography does not work successfully.

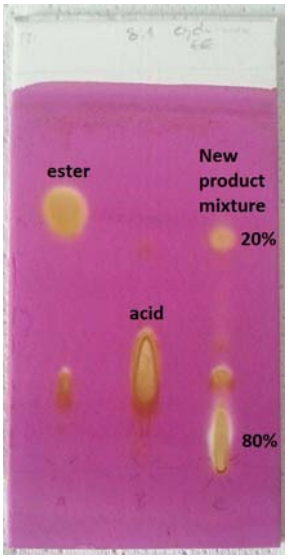


Figure 14: TLC for the research of the new product

To prove that the new structure does not have an acidic structure more investigations are performed. A solution of the reaction mixture in cyclohexane is washed several times with sodium hydroxide (1M) - but no substance is extracted. The exact same quantity of the products remains in the organic phase with the same GC-MS spectrum. With this experiment it is to conclude that the unknown compound does not have a carboxylic structure.

Comparing the MS spectrum of this unknown compound with the MS of the acid **7** it is also verified that a new product is obtained. Although it has a similar retention time as the acid, the fragmentations and peak shape of the compounds are different. The Mass spectra of both compounds are illustrated below. There is no prenyl group (m/z = 69), basis peak in the acid, in the new product. The total molecular weight of the new compound is m/z=167, less one hydrogen than of the acid **7**.

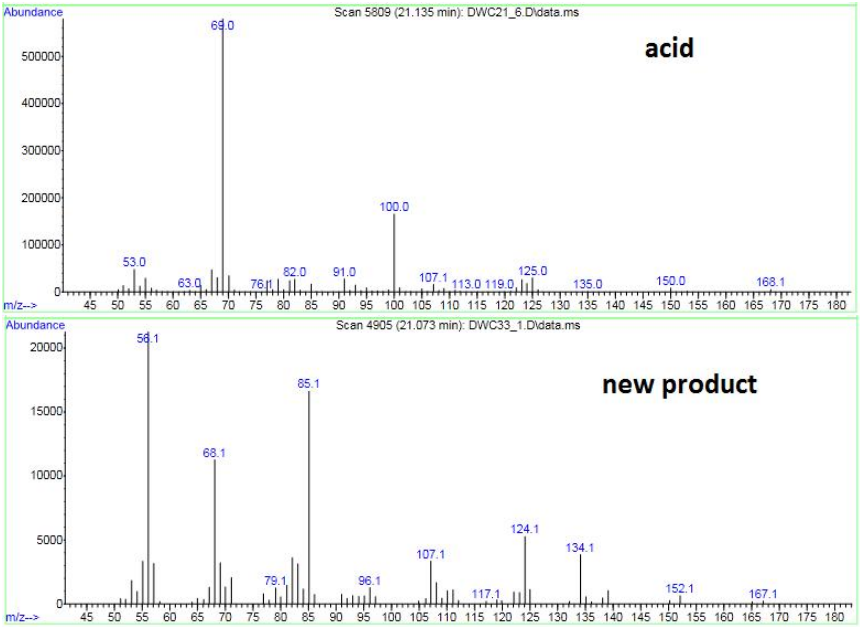


Figure 15: MS of the acid and of the new product

The mixture of the unknown products is also analysed by ^{1}H-NMR and ^{13}C-NMR. In the quantitative ^{13}C-NMR several peaks are seen with mainly two different integration levels, one of around 5, the other of around 1. Consequently the main two products are classified with a ratio of around 80% to 20%. They have both ten carbon atoms, three of them are tertiary carbon atoms. From the DEPT-^{13}C-NMR it is possible to know that both have three CH_3 groups, three CH_2 groups and one CH group.

In the case of the main product there is no evidence that a double bond or a carbonyl group exists in the structure. In the ^{13}C-NMR, the peak observed at 122 ppm can be related to a nitrile group. At 72 ppm a peak is seen which can be attributed to a secondary CH group, this carbon atom has no double bond linked to it. This phenomenon can also be observed in the ^{1}H-NMR, a peak for a secondary CH bond is located at 3.5 ppm in the deep field. Normally simple

CH bonds linked to alkanes are located at 1.4 ppm, but when they are bonded to hydroxyl groups the signal is shifted to 3.7-4 ppm. Therefore, it is possible to assume that the new structure contains a nitrile and a hydroxyl group, located on a secondary carbon atom bonded to one hydrogen atom. It can also be observed that two CH_2 groups show a double doublet signal in ^{1}H-NMR, implying that they are adjacent but not chemical equivalent. This means they are situated in a fixed structure, suggesting that the new compound has a cyclic structure. From the IR spectrum analysis of the mixture and compared with the acid **7** it was also verified the existence of a nitrile group at 2235 cm^{-1} and the absence of a carbonyl group at 3328 cm^{-1}.

The research of the synthesis of this new product with all indications from NMR and GC-MS and the following mechanism is developed - referred in *Figure 16*. While stirring Neronil **3** with 50% aqueous sulfuric acid, a cyclisation as main reaction is observed and 2,5,5-trimethyl-2-cyano-cyclohexanol **12** as a product is formed.

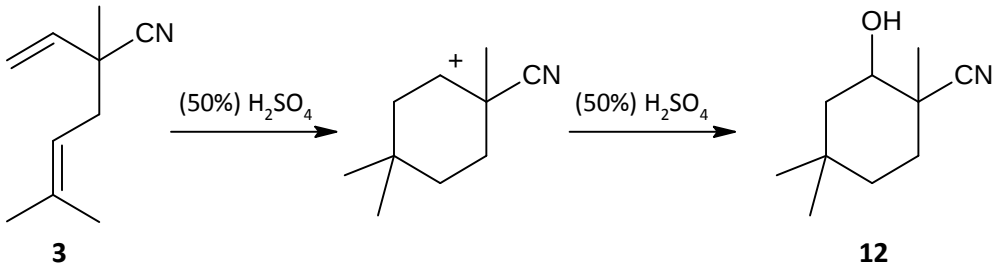
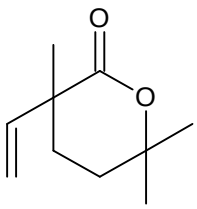


Figure 16: Synthesis of the new main product

The structure of the side products in the amount of 20% has also been checked. The analysis of the side products in the ^{13}C-NMR spectrum shows one signal at 175 ppm that is related to a carbonyl group. Two signals for a vinyl group are detected; one at 142 ppm for CH group and the other at 113 ppm for CH_2 group, but there is no evidence of the double bond in the prenyl rest. As there is no signal for the nitrile group but for a carbonyl group, it is assumed that the cyano group is hydrolysed to an acidic structure. With all this information it can be presumed that the new compound is formed by cyclisation reaction of the carboxyl group with the prenyl rest to form 2,5,5-trimethyl-2-vinyl-1,5-lactone **13 -** as illustrated in *Figure 17*.



13

Figure 17: Lactone structure of the side compound

Lactones are very stable products under acidic conditions. Linstead and Rydon had synthesised lactone from unsaturated acids by treating them with heat or mineral acids [47]. The lactonisation is performed with 60% aqueous sulfuric acid at a temperature of 30 °C, after one minute, the second layer disappears and after 15 minutes the starting material is converted at 96% into lactone. Another research by Yates and Kaldas proved an acid-catalysed formation of lactones from 2-hydroxynorbornane-2-acetic acid. This lactonisation is realized by stirring the acid with concentrated sulfuric acid for a period of 26 hours without any external heat [48].

This procedure shows that the hydrolysis of Neronil **3** to the corresponding acid cannot be performed under acidic conditions, because cyclisation reactions are much faster. The cyano group still exists in the main product. The vinyl group and the prenyl rest are very reactive structures. In the case of **12,** both groups react with each other to form a substituted cyclohexanol. For the formation of compound **13** first a hydrolysation of the nitrile group is needed, afterwards the formed acid reacts with the prenyl rest to form a lactone.

3.3. Synthesis of the ester

For the synthesis of 2,5-dimethyl-2-vinyl-4-hexenoic acid isobutyl ester **8** a direct esterification of the synthesized 2,5 -dimethyl-2-vinyl-4-hexenoic acid **7** is carried out. For the reaction the acid **7**, the alcohol isobutanol and p-toluenesulfonic acid as catalyst are mixed together in cyclohexane as solvent. The reaction mixture is heated under reflux and the formed water removed from the reaction by the solvent and separated in the Dean-Stark-apparatus. The reaction is performed without any problems and after only four hours the conversion of the acid **7** is already 100%. After the reaction work-up the ester **8** has a purity of 80% in GC-MS. The new compound is identified and checked by GC-MS and ^{1}H-NMR analyses and proven to be 2,5-dimethyl-2-vinyl-4-hexenoic acid isobutyl ester **8**.

The problem of this synthesis is located in the isolation procedure of the product. While performing the vacuum distillation, after some time a new product is found in the receiving flask, which increases in quantity during the distillation. In the first and second receiving flask of the distillation the amount of this product is between 10% and 14%, in the next flask the amount reaches 37-50%. This side product has a different retention time in GC-MS, also a different fragmentation but the same molecular weight as ester **8**.

As seen the performing of the synthesis of the ester is very easy and efficient in a very short period of time. The reaction is completed after four hours with a purity of 80%. During the distillation side-effects like the formation of new products occur.

3.4. Cope-rearrangement of 1,5-dienes

3.4.1. Neronil

The first research in Cope-rearrangements is executed with Neronil **3.** The goal is to synthesise 2,5,5 –trimethyl-2,6-heptadienenitrile **9 -** as illustrated in *Figure 18*. To accomplish the synthesis various procedures with different parameters like temperature, solvent, pressure and reaction time are applied.

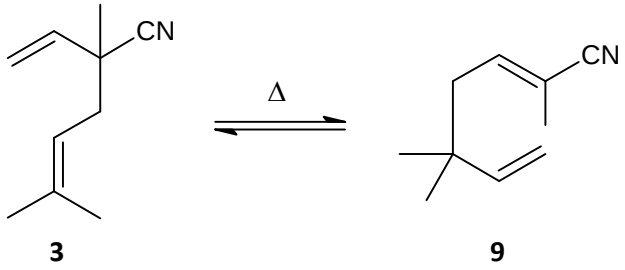


Figure 18: Cope-rearrangement of Neronil

The first Cope-rearrangement syntheses of Neronil are carried out with normal pressure. For this, the raw-material **3** is mixed in different solvents, heated up under reflux and the progress of the reaction is followed by GC-MS. All experiments are referred in *Table 2*. Using p-xylene as a solvent, only 2% of Neronil is converted after two days. This is an indication that the temperature for the rearrangement is not sufficient. The solvent is replaced by propylene carbonate (PC) which has a higher boiling point, at 220 °C. With this solvent, Neronil **3** is converted after only half a day in an amount of 26% of Cope-product **9**. A longer reaction time does not lead to a higher conversion, the amount of Cope-product remains at 26-28%.

Table 2: Cope-rearrangement of Neronil without pressure

Solvent	Temp. (°C)	Reaction time (h)	GC-MS results (%)			
			Neronil (3)	Cope product (9)	Side products	Relation Neronil-Product
p-xylene	140	27	93	1	5	98 : 2
PC	220	12	71	24	5	74 : 26
PC	220	23	64	26	11	72 : 28

The new product formed by heating up the Neronil is assumed to be the Cope-rearrangement product. The reason for this statement is the very similar retention time in GC-MS. Also, the molecular mass is the same, only the fragmentation of each one is different which confirms to be a Cope product.

The Cope-rearrangement is executed in a closed recipient to increase the amount of the Cope- product and reduce the reaction time while raising the pressure of the reaction. The results achieved are referred in *Table 3*.

In one procedure, the Cope- product is synthesised in a glass tube with a PTFE screw cap. In these experiments, different solvents with the concentration of 1:10 of Neronil to the solvent are tested. Subsequently different reaction temperatures are performed while heating up the reaction in a hot silicone oil bath but it has been impossible to ensure a constant temperature during the reaction. As the temperature and consequently the pressure of the reaction is rising, the amount of product **9** also increases, but the conversion of Neronil remains at the maximum of 30%. By using n-hexane as a solvent in experiment 4, the pressure of the reaction at a temperature of 150°C rises to 7.6 bar (estimated), but no reaction occurs. It is concluded, that the reaction needs a combination of a high pressure and high temperature to be successful. A solvent with a higher boiling point is essential for this synthesis, as performed in the experiment 5 and 6.

Table 3: Cope-rearrangement of Neronil with pressure

Exp.	Solvent	Temp. (°C)	Press. (bar)	Reaction time (h)	GC-MS results (%)			
					Neronil (3)	Cope product (9)	Side products	Relation Neronil-Product
4	n-hexane	150	7.6 *	142	97	2	1	99 : 1
5	p-xylene	200	4.2 *	171	77	22	1	78 : 22
6	PC	210	0.5 *	96	67	31	3	69 : 31
7	-	210		71	71	26	4	73 : 27
		233		166	63	27	1	70 : 30
8	cyclohexane	160	6.7 *	168	82	15	3	84 : 16
				234	80	18	3	82 : 18
9	p-cymene	235	3.5 *	43	69	25	7	73 : 27
				168	56	26	18	69 : 31
10	p-xylene	209	5.1 *	117	73	26	1	74 : 26
		231	7.3 *	262	23	15	62	62 : 38
11	p-xylene	210	5.1 *	4	80	16	4	82 : 18
		210	5.1 *	24	71	20	9	78 : 22
		210	5.1 *	72	68	24	9	74 : 26
		210	5.1 *	120	65	23	12	74 : 26
		210	5.1 *	168	64	23	13	74 : 26
		234	7.7 *	240	28	14	58	65 : 35
		234	7.7 *	288	15	10	75	59 : 41
		234	7.7 *	336	9	10	82	48 : 52

*estimated pressure [49], [50]

As the oil bath temperature is limited to 180°C, the reaction is carried out with different procedures. Neronil in small sealed glass ampoule, pure or in a solvent, is heated in an oven - as referred in *Table 3,* experiments 7 to 11. The use of an oven provides the advantage of higher and constant temperatures during the reaction.

In experiment 7 the conversion of pure raw material is tested. Samples are heated at temperatures of 210 °C and of 233 °C. The conversion of Neronil is of only 27% after three days and 30% after one week which means that there is no significant alteration in the process of the conversion, even after a longer reaction time. A possible explanation is, that when heating an ampoule, the high boiling point of Neronil prevents the pressure to rise sufficiently, and consequently the reaction does not continue.

The final attempt was to heat up the Neronil **3** with a solvent in an oven. Solutions of Neronil in different solvents in an equivalent of 1:10 are prepared and heated up to different temperatures - results are shown in experiment 8-11. As proven before, while using n-hexane with a boiling point of 69°C the reaction has a poor progress. Although, using cyclohexane, with the boiling point of 81°C, the conversion of Neronil rises up to 15% in comparable times. By the application of p-cymene or p-xylene as solvents the results from the other rearrangements are verified; the Cope-rearrangement product is formed constantly in an amount between 27% and 30%. It seems that after getting a conversion of Neronil at around 30%, no further rearrangement takes place or the reaction reaches an equilibrium state, but when the samples remain under high temperature, formation of side products occurs.

For a better research of the reaction performance relatively to time is checked when p-xylene as solvent is mixed with Neronil in an equivalent of 1:10, heated in an oven several times at different temperatures – as indicated in experiment 11. These attempts show similar results as the other experiments. At 72 hours with 210 °C the conversion achieves a maximum and only a moderate formation of side products is noticed. Nevertheless, an increasing after 7 days of the temperature to 234°C speeds up the decomposition of mainly Neronil.

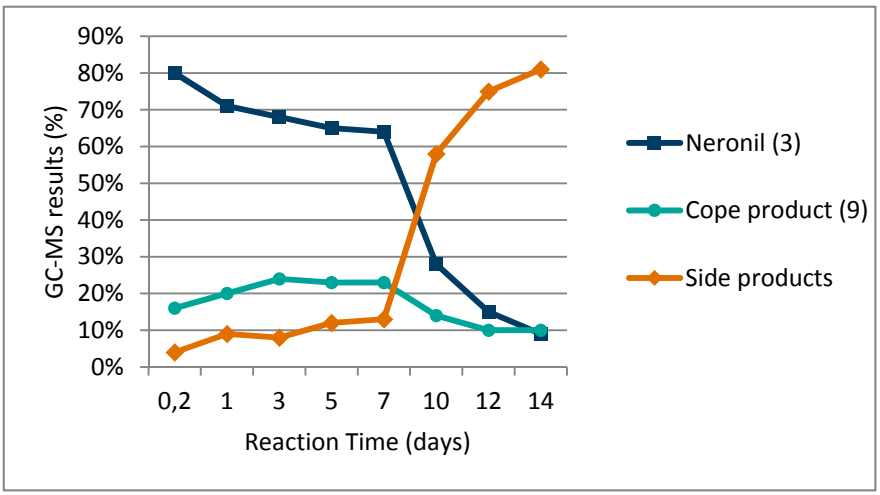


Figure 19: Cope-rearrangement of Neronil in p-xylene in experiment 11

To illustrate the conversion and decomposition reactions of Neronil **3** and the Cope product **9** in function to the reaction time, the *Figure 19* was created. After only four hours of reaction time the product **9** is formed in an amount of 18%, and is still increasing while the reaction continues. However, after three days the reaction stabilizes at a conversion of Neronil of 26%. After 1 week, when the temperature rises to 234°C, the proceeding of the reaction is no longer successful and mostly Neronil is destroyed into several side products.

This rearrangement of Neronil has not been as successful as planned. At the end of the procedure Neronil is still the principal compound in the reaction mixture, reaching a sort of equilibrium with the new product, shifted to the side of educts. For a theoretical explanation the enthalpy of formation for the reaction was calculated with energy data from literature [51]. The estimated enthalpy for the Cope rearrangement is -5 KJ/mol. This means that the reaction should be favourable to the Cope product, but only a small gain of energy in the reaction is achieved. This could be an explanation for the stabilisation of the conversion at around 26% amount of Cope product.

The different procedures had no influence on the results of the synthesis of the cope product. In all procedures the final conversion is always of about 27-31%. However, the simplest and most efficient procedure is proven to be the procedure where the raw material with a high boiling solvent is added into a sealed glass ampoule and heated in an oven at 210°C. In the Cope-rearrangement reactions the main parameters that influence the process of the synthesis are temperature and pressure. It is proven that the polarity of the solvents used during conversion has no influence on the results of the synthesis.

The best results of conversion are achieved in experiment 6. Neronil **3** is converted at 31% to 2,5,5 –trimethyl-2,6-heptadienenitrile **9** and not many products are formed. However, it has not been possible to separate the Neronil from the Cope product for a precise analysis of the structure, neither by distillation nor by flash chromatography.

3.4.2. Acid

The Cope-rearrangement of 2,5-dimethyl-2-vinyl-4-hexenoic acid **7** to produce 2,5,5-trimethyl-2,6-heptadienoic acid **10** is investigated with the procedures most successfully evaluated in conversion of Neronil.

For that, the raw-material **7** is placed in an ampoule with p-xylene as solvent with an equivalent of 1:10 (acid:solvent); the reaction vials are sealed and heated in the oven at two different temperatures, 160 ºC and 210 ºC. Additionally a second attempt is performed heating the acid **7** in p-xylene under reflux.

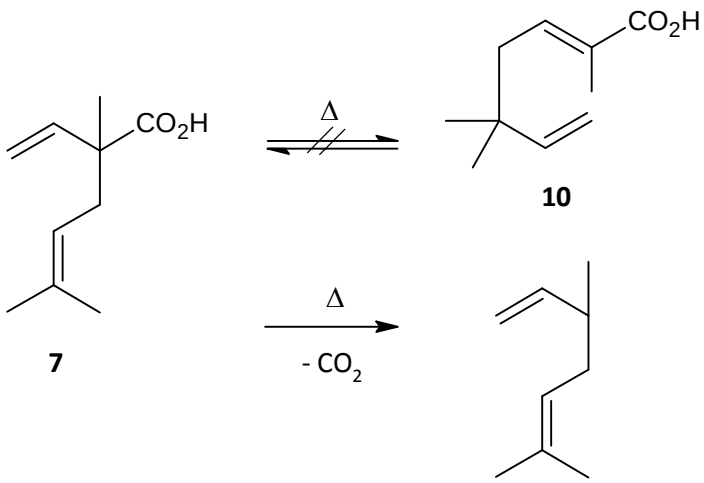


Figure 20: Decarboxylation of the acid

This reaction is not successful and no Cope-rearrangement product is formed. Analysing the progress of the reaction by GC-MS clarifies that the raw material is decomposed by heating. One explanation is that the acid **7** releases a carbon dioxide molecule and the alkane 5-methyl-2-vinyl-4-hexene is formed - as illustrated in *Figure 20*.

Investigations of the thermal decarboxylation of unsaturated acids had been already examined. Therefore, Arnold and co-workers studied the decomposition of a series of acids. For example 2,2-dimethylbuten-3-oic acid was heated over night at 260 °C and as a product 2-methylbutene-2 was formed. Alternatively, the same acid was heated in a sealed tube for five hours at 250 °C and only 25% of the unsaturated acid remained [52] [53]. Bigley checked twelve unsaturated acids in order to study their mechanism of the thermal decarboxylation, he showed the process to be a cyclic intramolecular one [54].

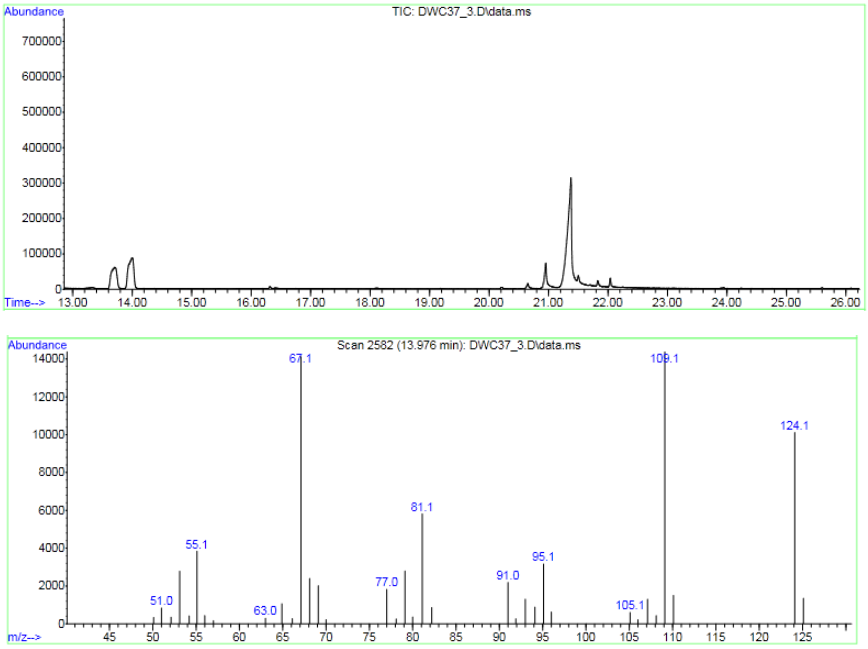


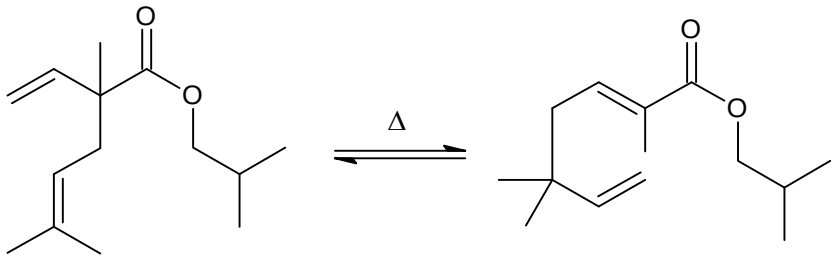
Figure 21: GC-MS of decarboxylation of the acid

In the GC-MS spectrum illustrated in *Figure 21*, after one day of reaction the acid **7** still exists at a retention time of 21 minutes and two new peaks at a retention time between 13 and 14 minutes are formed. Both compounds have a molecular mass of 124 g/mol, 44 less than the acid, matching a loss of carbon dioxide.

For this reason a treatment of the unsaturated acid **7** with high temperatures does not result in a Cope-rearrangement. The only further option to synthesise the Cope product **10** could be a catalytic reaction in order to lower the reaction temperature dramatically and therefore to suppress the decarboxylation of the acid.

3.4.3. Ester

To synthesise 2,5,5-trimethyl-2,6-heptadienoic acid isobutyl ester **11** a Cope-rearrangement performance of 2,5-dimethyl-2-vinyl-4-hexenoic acid isobutyl ester **8** is realized - referred in *Figure 22*. Regarding the procedures with Neronil it was concluded that the Cope rearrangement experiments with the best results are rearrangement reactions under pressure.



8 **11**

Figure 22: Cope-rearrangement of ester

Therefore the raw-material **8** in p-xylene with an equivalent of 1:10 is added into a glass tube with a PTFE screw cap, the vessel is closed and the reaction, with a use of hot silicone oil bath, heated to 140 °C. Because after four hours only 1% of Cope product has been formed, the reaction temperature is raised to 160 °C. And after further 4 hours as a result a higher conversion is achieved - as referred in *Table 4*. Since the reaction is proceeding for more than one week and only 55% of ester has converted, this synthesis is stopped. Although the amount of side products in experiment 1 is rather small, a higher reaction temperature is needed in order to speed up the performance of the reaction.

Table 4: Cope-rearrangement of ester

Exp.	Solvent	Temp. (°C)	Press. (bar)	Reaction time (h)	GC-MS results (%)			
					Ester (8)	Cope product (11)	Side products	Relation ester-Product
1	p-xylene	140	1.1*	4	95	1	4	99 : 1
		160	1.8*	8	93	3	4	98 : 2
				24	85	9	6	90 : 10
				48	76	16	8	82 : 18
				144	48	40	10	54 : 46
				192	41	48	11	44 : 55
2	p-xylene	210	5.1*	4	25	50	25	33 : 67
				24	16	61	23	22 : 78
				32	16	61	23	22 : 78
				48	16	61	23	22 : 78
				72	16	61	23	22 : 78
				96	16	61	23	22 : 78
3	p-xylene	233	7.7*	4	20	61	19	25 : 75
				24	15	47	38	24 : 76
				48	12	38	50	24 : 76
				72	8	24	68	24 : 76
				96	3	24	73	24 : 76
4	-	233		4	20	64	16	25 : 75
				24	19	61	20	24 : 76
				48	19	59	22	24 : 76
				72	18	59	23	24 : 76
				96	18	54	28	24 : 76

* estimated pressure [49]

Therefore further experiments are realized at two higher temperatures, 210 °C and 233 °C. The substance was solved in p-xylene, sealed in a glass ampoule and heated in an oven for at least 96 hours where a maximum conversion with an average of 78% is achieved. At a temperature of 210°C the reaction stabilized after one day and the amount of Cope product from there on did not increase anymore. At 233°C the conversion was nearly finished after 4 hours. A similar behaviour has also been noticed in the Cope-rearrangement of Neronil **3**. Although more side products, up to 73%, are formed at 233°C, the amount of side products at a temperature of 210°C was stabilized at 23%.

Another experiment is carried out where the raw material without solvent is added in small ampoules and heated to 233 °C in an oven. After only four hours the conversion of the

ester **8** amounts to 75% of product **11** and stabilizes at 76% after one day. The amount of side products is not very high.

In order to visualise the performance of the Cope-rearrangement of the ester **8** in function of the temperature, experiment 1 (*Figure 23*) and experiment 2 (*Figure 24*) are being confronted. It is obvious that the amount of ester **8** decreases while the amount of Cope product **11** and side products rises. The conversion as seen is much faster when the temperature is above 200 °C. Only one day is needed to reach a conversion of 78%, but using a temperature of 160 °C the reaction takes more than one week to be nearly completed.

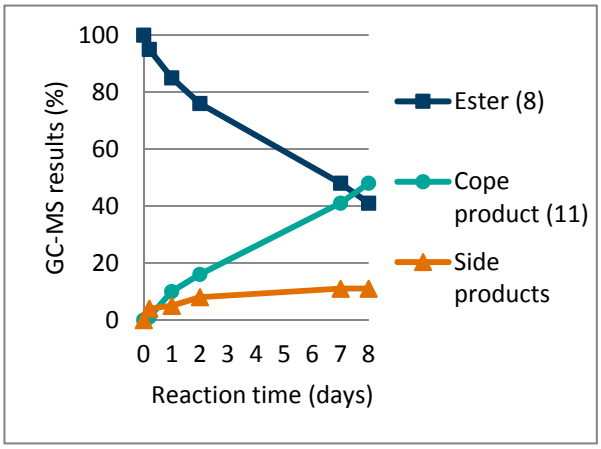


Figure 23: Cope-rearrangement of ester at 160 °C

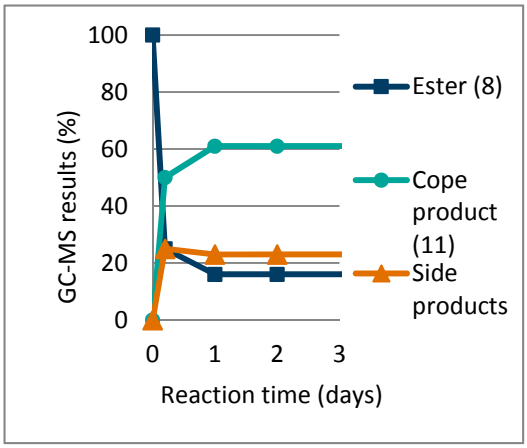


Figure 24: Cope-rearrangement of ester at 210 °C

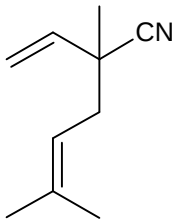
As in the Cope-rearrangement of Neronil, the enthalpy of formation for the synthesis is estimated with energy data's from literature [51] too and is calculated with -15 KJ/mol. This verifies the results from all the reactions that have been examined. As expected from the calculated enthalpy, the Cope-Rearrangement product of the ester **8** is more stable than the educt and is produced in a higher quantity than Neronil. In both cases the reaction is stabilised. The only difference is that ester has a higher percentage, 78% of the Cope product **11** is formed. Even when the reaction temperature is 160 °C the balance between the educt and product is shifted to the product side as expected from literature.

When comparing the amount of Cope product of Neronil and of ester, the ester Cope product **11** is achieved in a higher quantity than the Neronil Cope product **9.** These results match with the predicted enthalpy from each formation reaction. There is an energy gain for conversion Neronil **3** to **9** of 5 KJ/mol and for conversion ester **8** to **11** of 15 KJ/mol. Therefore, in the case of the Cope-rearrangement of ester the reaction equilibrium is being shifted to the product side and in the rearrangement of Neronil is on the educt side. The structure of Cope ester **11** has been verified with ^{13}C-NMR and ^{1}H-NMR, making it possible to assume that the structure of Cope Neronil **9** is also correct.

However, for rearrangement of the ester the best performance is achieved by using p-xylene as a solvent at a temperature of 210 °C where the 2,5,5-trimethyl-2,6-heptadienoic acid isobutyl ester **11** is formed in an amount of 78% after one day.

4. Experimental Part

4.1. Synthesis of 2,5-dimethyl-2-vinyl-4-hexenenitrile 3



3

Procedure I: First 0.003 mol (1.02 g) of tetrabutylammoniumbromid, 0.504 mol of the base (28.3 g of potassium hydroxide powder or 20.1 g of sodium hydroxide tablets) and 80 mL of the solvent (cyclohexane or n-hexane) are mixed in a 250 mL-three-neck-flask and stirred intensively with a KPG stirrer. After the temperature of 10 °C is stabilized with an ice water bath, 0.315 mol (31.5 mL) of 2-methyl-3-butenenitrile is added drop wise to the mixture, while keeping its temperature between 10 and 20 °C. Next the temperature of the reaction is elevated to 35/45 °C and then 0.410 mol (46.9 mL) of prenylchloride is dropped slowly into the reaction mixture. After ending the addition of prenylchloride the reaction mixture is stirred constantly at a temperature of 60 °C. To get a more stable temperature a heating mantle can be used instead of a hot water bath.

Procedure II: In a 250 mL-three-neck-flask 0.003 mol (1.02g) of tetrabutylammonium-bromid, 0.315 mol (31.5 mL) of 2-methyl-3-butenenitrile, 0.410 mol (46.9 mL) of prenylchloride and 80 mL of cyclohexane are added. Next the mixture is heated to a temperature of 60°C with a hot water bath. 0.504 mol (20.1 g) of sodium hydroxide tablets is added to the reaction mixture in small quantities hour after hour, according to the reaction development.

Procedure III: First, 0.003 mol (1.02g) of tetrabutylammoniumbromid, 0.504 mol of the base (28.3 g of potassium hydroxide powder or 20.1 g of sodium hydroxide tablets) and 80 mL of the solvent (cyclohexane or n-hexane) are mixed and stirred in a 250 mL- three-neck-flask. Using a heating mantle, the temperature is raised to the boiling point of the solvent. Next, a mixture of 0.315 mol (31.5 mL) of 2-methyl-3-butenenitrile and 0.410 mol (46.9 mL) of prenylchloride is added drop wise to the reaction, approximately one drop per second. The water formed during the reaction is separated with the Dean-Stark apparatus.

Figure 25: Neronil experiment equipment for procedure I & II (left) and for procedure III (right)

To follow the reaction progress, samples for the GC-MS measurements are prepared. One millilitre of the reaction solution is placed into a small separation funnel and washed with 1 mL of distilled water. The organic layer is separated from the water one and dried with sodium sulfate. Next a sample for the GC-MS is prepared taking 20 µL from the dried organic layer and mixed in 10 mL ethanol. From that solution 100 µL are added to 900 µL of ethanol in a small GC vial.

Work up: The reaction solution is decanted from the solid base in a separation funnel. The remaining base in the reaction flask is washed twice with 30 mL of the same solvent used in the reaction and added to the organic layer in the funnel. This mixture is washed twice with 30 mL of distilled water. After the second washing, the pH value of water is checked. If the value is neutral the work up procedure can proceed. If the pH value is acid the organic layer is washed with 20 mL of 5% - sodium bicarbonate solution until it is neutral. If it is basic, it is washed with 0.1 M – hydrochloric acid until it is neutral. The layers are separated and the organic layer is dried with sodium sulfate.

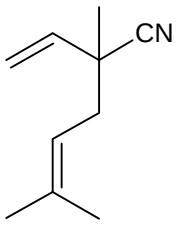
Isolation: First the solvent is removed from the reaction mixture in a rotary evaporator. The distillation of cyclohexane is executed at 40 °C water bath temperature and with a reduced pressure of 235 mbar, n-hexane is removed at 40 °C at 335 mbar. [55] The raw product is purified in a second distillation. It is necessary to distil under reduced pressure - the apparatus is illustrated in *Figure 26* - because of the high boiling point of Neronil. First the remaining solvent and the starting material are evaporated and collected. The isolation of Neronil elapses under a pressure of 20 mbar with a temperature of 80 °C and a yield with an average of 30-46%.

Figure 26: Normal distillation equipment to isolate product

Characterization

Main product:

- 2,5-dimethyl-2-vinyl-4-hexenenitrile **3** [Neronil]



Appearance: Colourless liquid

Molecular Formula: $C_{10}H_{15}N$

MS (EI, 70 eV, 250 °C): m/z (%) = 149 (M^+), 81 ($C_5H_7N^+$,6), 69 ($C_5H_9^+$,100), 53 ($C_3H_3N^+$,9)

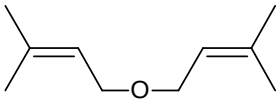
Density: 0.9 g/mL

Boiling Point: 61 °C (1.2 mbar) 228 °C (1 bar)

RT in the GC: 18.2 min

Side products:

- bis (3-methylbut-2-en-1yl) ether **5** [Ether]



Appearance: Colourless liquid

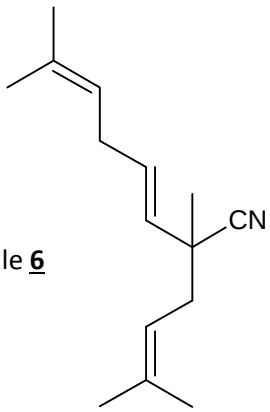
Molecular Formula: $C_{10}H_{18}O$

MS (EI, 70 eV, 250 ºC): m/z (%) = 154 (M^+), 139 ($C_9H_{15}O^+$,59), 85 ($C_5H_9O^+$,40), 69 ($C_5H_9^+$,100), 55 ($C_4H_7^+$,23)

Density: 0.8 g/mL

Boiling Point: 56 ºC (10 mbar)

RT in the GC: 18.8 min



- 2,7-dimethyl-2-(3-methylbut-2-en-1-yl-)-octa-3,6-dienenitrile **6**

Appearance: Yellow liquid

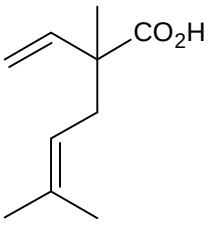
Molecular Formula: $C_{15}H_{23}N$

MS (EI, 70 eV, 250 ºC): m/z (%) = 217 (M^+), 148 ($C_{10}H_{14}N^+$,31), 94 ($C_7H_{10}^+$,17), 69 ($C_5H_9^+$,100)

Boiling Point: 124 ºC (0.19 mbar)

RT in the GC: 24.8min

4.2. Synthesis of 2,5-dimethyl-2-vinyl-4-hexenoic acid 7



7

Procedure I: In a 100 mL-two-neck-flask, 0.75 mol (30 g) of sodium hydroxide and 42 mL of distilled water are mixed, resulting in a 25% aqueous sodium hydroxide solution. Next, 0.1 mol (15 g) of pure Neronil **3** is added to the solution. The reaction is refluxed until no more ammonia escapes, which can be seen by checking the pH value on the top of the reflux condenser [21]. This experience can also be realized, adding 0.36 mol (20 mL) of ethylene glycol as a solubilising solvent.

To follow the reaction progress, samples for the GC-MS measurements are prepared. One millilitre of the reaction were neutralized with sulfuric acid and then added to a small separation funnel where the solution is extracted with 1 mL of cyclohexane. The organic phase is separated and dried with sodium sulfate. The sample for the GC-MS is prepared as explained in chapter 4.5.1..

Procedure II: In a 100 mL-two-neck-flask, a solution of 0.16 mol (9 g) of potassium hydroxide and 1.6 mL of distilled water is placed. In this 85% aqueous potassium hydroxide

solution, 40 mL of ethylene glycol is mixed well. Next, 0.05 mol (7.5 g) of Neronil is added to the solution, which is heated under reflux for five to six hours [56].

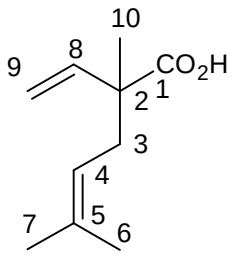
For observing the reaction, GC-MS samples were taken. 1 mL of the solution is added to 5 mL of distilled water to dissolve the ethylene glycol in it. Next, about 3.5 mL of hydrochloric acid (1M) is added until the solution is slightly acidic. After that the watery mixture is extracted twice with 3 mL of cyclohexane and the organic phase is dried with sodium sulfate. Before the sample is prepared as usual, the cyclohexane is removed in a rotary evaporator.

Work up: The reaction mixture is neutralized with 50% aqueous sulfuric acid, the final pH value has to be slightly acidic. If ethylene glycol is used during the reaction, the solution is first dissolved in 150 mL of distilled water. Then the solution is added in a 1 L separation funnel and extracted thrice with 75 mL of ethyl acetate. The combined organic layers are dried with sodium sulfate and distilled in a rotary evaporator to remove the ethyl acetate. In this final step, when almost all the solvent is removed, more 10 mL of ethyl acetate are added to the remaining ethyl acetate. The vacuum is set to the lowest point and in the end only the acid is remained in the flask.

Figure 27: Vacuum distillation equipment with capillary

Isolation: After the work up from the acid **7**, a small vacuum distillation is prepared. The acid is distilled at 10 mbar in a temperature of 80 °C. The apparatus is referred in *Figure 27*. The collected product is isolated with a yield of 80-96%, a GC-MS and a NMR analysis is prepared - as explained in chapter 6.5.

Characterization



- 2,5-dimethyl-2-vinyl-4-hexenoic acid **7** [acid]

Appearance: Colourless liquid

Molecular Formula: $C_{10}H_{16}O_2$

MS (EI, 70 eV, 250 °C): m/z (%) = 168 (M^+), 69 ($C_5H_9^+$,100), 53 (C_4H_5,8), 82 ($C_6H_{10}^+$,5), 123 ($C_9H_{15}^+$,5)

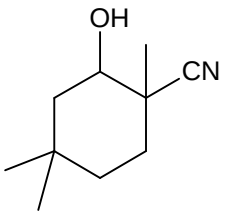
^{1}H-NMR (CDl_3, 400 MHz): 1.2 (s, 10-CH_3), 1.6 (s, 6–CH_3), 1.7 (s, 7–CH_3), 2.3 (dd, 3-CH_2), 2.4 (dd, 3-CH_2), 5.1 (m, 4-CH, 9–CH_2), 6.1 (dd, 8–CH)

Boiling Point: 80 °C (10 mbar)

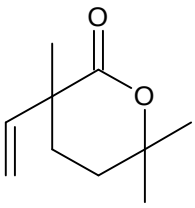
RT in the GC: 21.2 min

Formation of side product under acidic hydrolysis

- 2,5,5-trimethyl-2-cyano-cyclohexanol **12**
- 2,5,5-trimethyl-2-vinyl-1,5-lactone **13**



12



13

Procedure III: In a 100 mL-three-neck-flask, 0.1 mol (5 mL) of concentrated sulfuric acid is placed and 2 mL of distilled water are dropped into it. This solution is heated to a temperature of 80 °C, then 0.085 mol (12.7 g) of Neronil is added drop wise for half an hour. The reaction is stirred at 80-90 °C until the end of the reaction. The apparatus is illustrated in *Figure 20,* left [3].

To prepare a sample for GC-MS, 1 mL or 1 g of reaction mixture is retrieved during reaction, depending on its viscosity. Then the solution is neutralized with sodium hydroxide (3M) and afterwards extracted twice with 5 mL of ethyl acetate. The organic phase is dried with sodium sulfate, next the ethyl acetate is removed from the sample in a rotary evaporator and a sample is prepared, as in chapter 4.5.1.

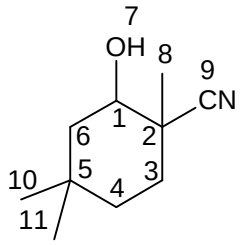
Procedure IV: In a 100 mL–Erlenmeyer flask, 0.03 mol (5 g) of Neronil and 0.04 mol (5 g) 50% aqueous sulfuric acid are added and stirred constantly in room temperature. Depending on the progress of the reaction, a hot water bath with 50 °C can be added to speed up the reaction. The samples during the experiment are prepared as explained in the previous procedure III.

Work up: The reaction mixture is neutralized with about 10 mL of sodium hydroxide (3M). Then the solution is extracted twice with 10 mL of ethyl acetate. The combined organic layers are dried with sodium sulfate and distilled in a rotary evaporator to remove the ethyl acetate. When almost all solvent is removed, more 10 mL of ethyl acetate are added to the flask with the remaining ethyl acetate and the distillation is continued until complete.

Isolation: The same distillation can be performed as in the acid - illustrated in figure 27. In this case instead of a capillary tube, a thermometer is used. The distillation is performed with a vacuum of 7 mbar with a temperature of 105 °C.

Characterization

- 2,5,5-trimethyl-2-cyano-cyclohexanol **12** [cyclohexanol]



Appearance: Colourless liquid/viscose

Molecular Formula: $C_{10}H_{17}NO$

MS = 168 g/mol

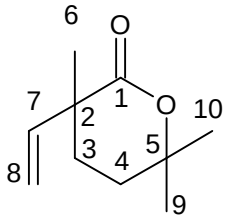
^{1}H-NMR (CDl_3, 400 MHz): 0.9 and 0.99 (s, 10, 11-CH_3), 1.3 (m, 4-CH_2), 1.4 (s, 8–CH_3), 1.6 (m, 6–CH_2), 1.8 (m, 3-CH_2), 3.5 (dd, 1–CH)

^{13}C-NMR (CDl_3, 100 MHz): 23 (s, 8-CH_3), 32 (d, 10, 11-CH_3), 32 (s, 5-C), 33 (s, 3–CH_2), 35 (s, 4-CH_2), 42 (s, 2-C), 45 (s, 6–CH_2), 72 (s, 1–CH), 122 (s, 9–CN)

Boiling Point: 105 ºC (7 mbar)

RT in the GC: 21.1 min

- 2,5,5-trimethyl-2-vinyl-1,5-lactone **13** [lactone]



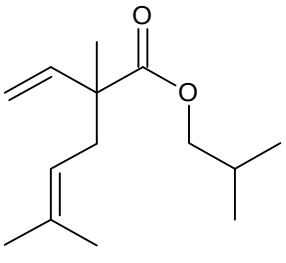
Appearance: Colourless Liquid/Viscose

Molecular Formula: $C_{10}H_{16}O_2$

^{13}C-NMR (CDl_3, 100 MHz): 25 (s, 6-CH_3), 30 (d, 4-CH_2), 32 (d, 9, 10-CH_3), 32 (d, 3-CH_2), 45 (s, 5–C), 113 (s, 8-CH_2), 142 (s, 7-CH), 175 (s, 1–C)

MS = 168 g/mol

4.3. Synthesis of 2,5-dimethyl-2-vinyl-4-hexenoic acid isobutyl ester 8



8

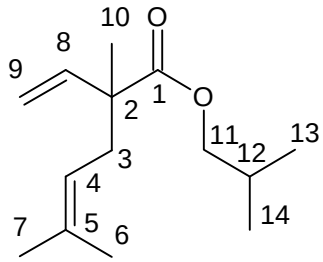
Procedure I: In a 250 mL–three-neck-flask, 0.04 mol (6.7 g) of the acid **7** is added, together with 0.04 mol (3 g) of isobutanol, 0.001 mol (0.17 g) of p-toluenesulfonic acid and 24 mL of cyclohexane. In the Dean-stark apparatus 15 mL of cyclohexane is additionally added to fill it up. The reaction is heated to the boiling point of the solvent, 81 ºC, and performed at this temperature until all water formed is removed. The apparatus is referred in *Figure 30* [57].

Work up: The solution is poured into a separation funnel and washed twice with 25 mL of distillated water. After that 20 mL of a 5% aqueous solution of sodium bicarbonate is added to neutralize the product solution. If there is not enough separation of the two phases, 5 mL of a saturated solution of sodium chloride is added. Finally the organic layer is dried with sodium sulphate and the solvent is removed from the product in a rotary evaporator [57].

Isolation: For the isolation of the ester **8** a small distillation similar, equipped with a nitrogen trap between the vacuum pump and the garget. The compound is distilled at a vacuum of 1 mbar and with a temperature of 80 °C. A yield of 47% is achieved. The apparatus is shown in *Figure 28*.

Figure 28: Vacuum distillation equipment to isolate the product

Characterization



- 2,5-dimethyl-2-vinyl-4-hexenoic acid isobutyl ester **8** [ester]

Appearance: Colourless liquid

Molecular Formula: $C_{14}H_{24}O_2$

MS (EI, 70 eV, 250 ºC): m/z (%) = 224 (M^+), 69 ($C_5H_9^+$,86), 100 ($C_5H_8O_2$,100), 81 ($C_6H_9^+$,13), 123 ($C_9H_{15}^+$,28), 57 ($C_4H_9^+$,17)

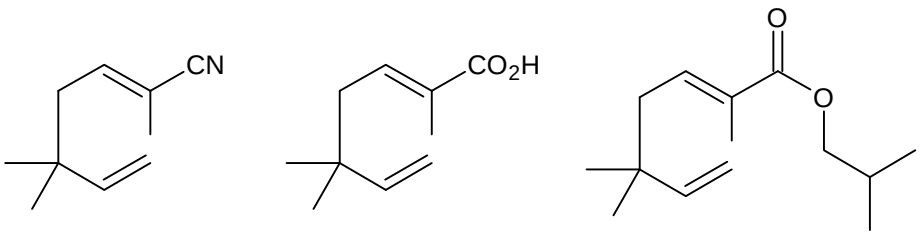
^{1}H-NMR (CDl_3, 400 MHz): 0.9 and 0.92 (s, 13, 14-CH_3), 1.23 (s, 10–CH_3), 1.58 (d, 6–CH_3), 1.67 (s, 7–CH_3), 1.9 (m, 12–CH), 2.4 (d, 3-CH_2), 2.7 (d, 3-CH_2), 3.8 (d, 11–CH_2), 5.1 (m, 4-CH, 9–CH_2), 6.1 (m, 8–CH)

Boiling Point: 80 ºC (1 mbar)

RT in the GC: 22.4 min

4.4. Cope-rearrangement of 1,5-dienes

- 2,5,5–trimethyl-2,6-heptadienenitrile **9**
- 2,5,5-trimethyl-2,6-heptadienoic acid **10**
- 2,5,5-trimethyl-2,6-heptadienoic acid isobutyl ester **11**



9 **10** **11**

Procedure I: In a glass ampoule, 0.5 g of pure Neronil **3**, acid **7** or ester **8** is added and then sealed with a hot gas flame. The ampoule is set aside to cool down for a few minutes and then checked if it is well sealed. Next the temperature in the oven is set up to 235 °C. When the temperature is reached, the ampoules are placed inside. More than one glass ampoule are prepared to follow the reaction over the time - as illustrated in *Figure 29,* left.

Procedure II: A solution of Neronil, acid or ester in two concentrations is sealed in a glass ampoule as in procedure I. The prepared concentrations have an equivalent of 1:1 (0.1 g of Neronil and 0.1 mL of the solvent) and an equivalent of 1:10 (1 g of Neronil and 10 mL of solvent). The solvents used in these experiments are referred in the experiment results. The ampoules are place in a preheated oven with a temperature of 210 °C, and taken out at different reaction times.

Procedure III: A glass tube is filled with a solution of 1g of Neronil, acid or ester in 10 ml solvent and closed well with a polytetrafluoroethylene screw plug - as shown in *Figure 29,* right. The tube is immersed in a silicone oil bath and heated to several temperatures in a range of 150-200 °C. The progress of the reaction is observed by GC-MS measurements.

Figure 29: Glass ampoules for procedure I & II (left), glass tube for procedure III (right)

Procedure IV: The assembly of this procedure is illustrated in *Figure 30*. In a 100 mL - two-neck-flask 1 g of Neronil, acid or ester a 10 mL solvent is added. The solution is heated to the boiling point of the solvent. The reaction is refluxed depending on the progress of the reaction.

Figure 30: Preparation of procedure IV

Procedures from I to IV are executed with different reaction times - from four hours until one week. When the reactions are finished, the samples for the GC-MS are prepared and the percentage of rearranged product is determinated. In case of reactions with only pure raw-material - procedure I - the GC-MS samples are prepared as usual, that means: 20 µL from the reaction is placed into 10 mL ethanol and from that solution 100 µL are taken and filled together with 900 µL ethanol in a small GC-MS vial. In case of diluted starting material 1:10, 20 µL from the reaction mixture is added to 10 mL of ethanol, that solution is used for measurements in GC-MS.

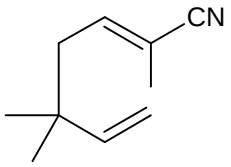
Isolation: To find a way of separation the Cope Product from the starting Neronil, acid or ester, the Thin Layer Chromatography is carried out. First a 1% solution from the reaction mixture in cyclohexane is prepared, the same is done with pure starting materials. Next 5 µL and 10 µL from the 1% solution of the several compounds are dropped on silica gel plates. The plates are placed in chambers with an eluting solvent mixture. The solvent is allowed to rise up the plate to 1 cm from the top und then removed and dried. As the separation is not visible at UV-light, the silicate plates are placed in an iodine chamber for around two minutes or immersed in a 5% aqueous solution of potassium permanganate. In the case of the experiences of Cope-rearrangement with Neronil and ester, the best eluting solvent mixture is 15:1 of cyclohexane to methyl-tert-butylether, where a separation from the corresponding Cope products, Neronil and ester is possible. The respective R_f values from Cope product **9** and Neronil are 0.44 and 0.55 and in the case of Cope product **11** and ester the R_f values are 0.58 and 0.70.

Figure 31: Flash Chromatography equipment

Next a Flash Column Chromatography is carried out with the equipment shown in the *Figure 31.* For that, a column of 40 g of silica gel is used, as well as the solvents n-hexane and acetone with a flow-rate of 40 mL/min, but the separation of the compounds could not be monitored because the products do not have absorption at the UV frequencies of 254 nm and 233 nm. With final GC-MS measurements after the FCC verifies that the separation of the compounds has not been successful.

Characterization

- 2,5,5 –trimethyl-2,6-heptadienenitrile **9** [Neronil cope]



Appearance: Orange Liquid

Molecular Formula: $C_{10}H_{15}N$

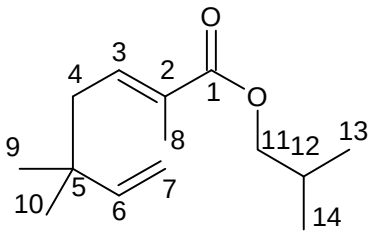
MS (EI, 70 eV, 250 ºC): m/z (%) = 149 (M^+), 81 ($C_5H_7N^+$,11), 69 ($C_5H_9^+$,100), 53 ($C_3H_3N^+$,13)

RT in the GC: 19.4 min

- 2,5,5-trimethyl-2,6-heptadienoic acid isobutyl ester **11** [ester cope]

Appearance: Colourless Liquid

Molecular Formula: $C_{14}H_{24}O_2$



MS (EI, 70 eV, 250 ºC): m/z (%) = 224 (M^+), 69 ($C_5H_9^+$,94), 100 ($C_5H_8O_2$,100), 156 ($C_9H_{16}O_2^+$,37), 123 ($C_9H_{15}^+$,7), 57 ($C_4H_9^+$,14)

^{1}H-NMR (CDl_3, 400 MHz): 0.93 and 0.95 (s, 13, 14-CH_3), 1.0 (s, 9, 10-CH_3), 1.8 (s, 8–CH_3), 1.9 (s, 12–CH), 2.2 (d, 4-CH_2), 3.9 (d, 11–CH_2), 5.0 (m, 7–CH_2), 5.8 (dd, 6–CH), 6.7 (t, 3–CH)

^{13}C-NMR (CDl_3, 100 MHz): 19 (d, 9, 10-CH_3), 20 (d, 13, 14-CH_3), 26 (s, 12-C), 27 (s, 8–CH_3), 37 (s, 5-H), 41 (s, 4-CH_2), 70 (d, 11–CH_2), 111 (d, 7–CH_2), 119 (s, 6–C), 140 (s, 3–C), 168 (s, 1–C)

RT in the GC: 23.3 min

4.5. Analytical Measurement

4.5.1. GC-MS

In this practice the samples for the GC-MS need to have a concentration of 200 ppm. To prepare the sample, 20 µL from the reaction solution is added to 10 mL of ethanol, resulting of a concentration of 2000 ppm. As a concentration of 200 ppm is needed, the previous solution needs to be diluted ten times, for that 100 µL from that solution is mixed with 900 µL of ethanol. The unknown sample of 1 mL is ready to be measured in the GC-MS.

Figure 32: GC-MS equipment

The samples are measured in the GC system 7890A and MS 5975C, made by Agilent Technologies [58]. The measurement conditions are referred in *Table 5* and the equipment is shown in *Figure 32*. The computer software used is chemstation and for comparing the measured spectrum with the already existing data, the database NIST2011 is applied.

Table 5: Equipment Details of the GC-MS

Inlets Details	
Injection Volume	1 µL
Filling Speed	2 µL/s
Injection to GC Speed	50 µL/s
Syringe Size	10 mL (54 mm Syringe of the Company PAL System accessories)
Cleaning Syringe	Pre clean twice with solvent (Ethanol) and twice with sample. After injection the sample Post clean twice with solvent
Temperature Injector	275 ºC
Pressure Injector	15.7 psi
Split Ratio	10:1
Column Details	
Column Size	30 m x 250 µm x 0.25 µm (HP-5 of the Company Agilent Technologies)
Carrier gas	Helium
Flow	1.5 mL/min
Pressure	15.7 psi
Average Velocity	33 cm/s
Oven Details	
Equilibration time	0.5 min
Programme	40 ºC for 10 min – 240 ºC with a rate of 10 ºC/min – 300 ºC with a rate of 20 ºC/min
Run Time	33 min for “Neronil” Method and 35 min for “Cope” Method
FID Details	
Heater	250 ºC
H2 Flow	35 mL/min
Air Flow	400 mL/min
Makeup Flow (He)	20 mL/min
Flame	15 pA
Extra Details	
Ion source	230 ºC
MS	Quadrupole – 150 ºC
Scan-rage	50-300 m/z
EI	70 eV
MSD Transfer Line	300 ºC

4.5.2. NMR-spectra

To prepare a sample for NMR analysis 10 to 50 mg of the component is filled in a NMR tube. Then 1 mL of chloroform - d_1 ($CDCl_3$) is added and the mixture is shaken well. The final concentration of NMR-sample should be: 10% volume of compound and 90% $CDCl_3$.

The equipment for the NMR analysis - AVANCE III^{TM} 400 MHz - is made by Brucker BioSpin GmbH and illustrated in *Figure 33*. The measurements conditions are mentioned in *Table 6.*

Table 6: Measurements Details of NMR

Test Conditions	
Nuclei Analyzed	^{1}H – Hydrogen or ^{13}C - Carbon
Operating Temperature	298 K
Operating Frequency	400 MHz for ^{1}H and 400 MHz for ^{13}C
Solvent	Reference locked to $CDCl_3$ at 7.24 ppm
Pulse Width	30 º
Pulse Delay	10 s
Number of scans	64

Figure 33: NMR equipment

5. Conclusions

In this work synthesis optimizations of substances with potential odoriferous properties have been carried out. In the beginning an overview of planned substances was presented; some new compounds could be synthesized based on the key substance Neronil **3**. The achieved synthesis results in this work are referred in *Figure 34.* Most of the target products could be obtained, only the Cope-rearrangement of the acid **7** was not achieved and also another unexpected product was formed when reacting Neronil **3** with sulfuric acid.

In order to improve the synthesis of 2,5-dimethyl-2-vinyl-4-hexenenitrile **3,** a new procedure, compared to the previous methods, was implemented. It was discovered that removing the water formed during the reaction could enhance the performance of the reaction. Based on this change in the procedure the yield was raised from 35% to 46% and a purity of 99% of Neronil was reached. As in the previous studies it was proven that when using sodium hydroxide as base less side products are formed.

The second field of this work was to convert the nitrile group of Neronil into other functional groups. Therefore a hydrolysis of this group under basic and acidic conditions was investigated. By a hydrolysis of **3** with potassium hydroxide in ethylene glycol the target 2,5-dimethyl-2-vinyl-4-hexenoic acid **7** is formed after five hours heating, with a yield of 96%. When adding sulfuric acid to Neronil a mixture of new products was formed. The first one is 2,5-dimethyl-2-vinyl-4-hexenoic acid **12**, as main product with around 80% and the second is 2,5,5-trimethyl-2-vinyl-1,5-lactone **13,** as a side product with around 20%. The esterification of the acid **7** leads to the functional group of esters. By heating the acid **7** with sulfuric acid and isobutanol a total conversion of the acid was achieved after four hours refluxing. The 2,5-dimethyl-2-vinyl-4-hexenoic acid isobutyl ester **8** was achieved with a yield of 47% and a purity of 80%. It was discovered that during the purification of the ester **9** by distillation a new product was formed. This product was identified to be a Cope rearranged one. The synthesis of the ester with acid and alcohol directly from the Neronil leat again to the mixture of **12** and **13** as explained before. The Cope-Rearrangement was found to be possible for two substances: Neronil **3** was transferred to 2,5,5 –trimethyl-2,6-heptadienenitrile **9** with a conversion of around 30% and ester **8** to 2,5,5-trimethyl-2,6-heptadienoic acid isobutyl ester **11** with a conversion of around 78%. Neither of them could be obtained as pure products. These results were confirmed by an estimation of enthalpy of formation from the cope products, where the Cope product **11** with an enthalpy of -15 KJ/mol has been more stable than the Cope product **9** with only -5 KJ/mol - as confirmed in the practical work. Finally in the case of the acid **7** the Cope-Rearrangement did not work instead a decarboxylation of the acid occurs.

All the new products synthesised were confirmed by GC-MS and verified by ^{1}H-NMR and ^{13}C-NMR analysis.

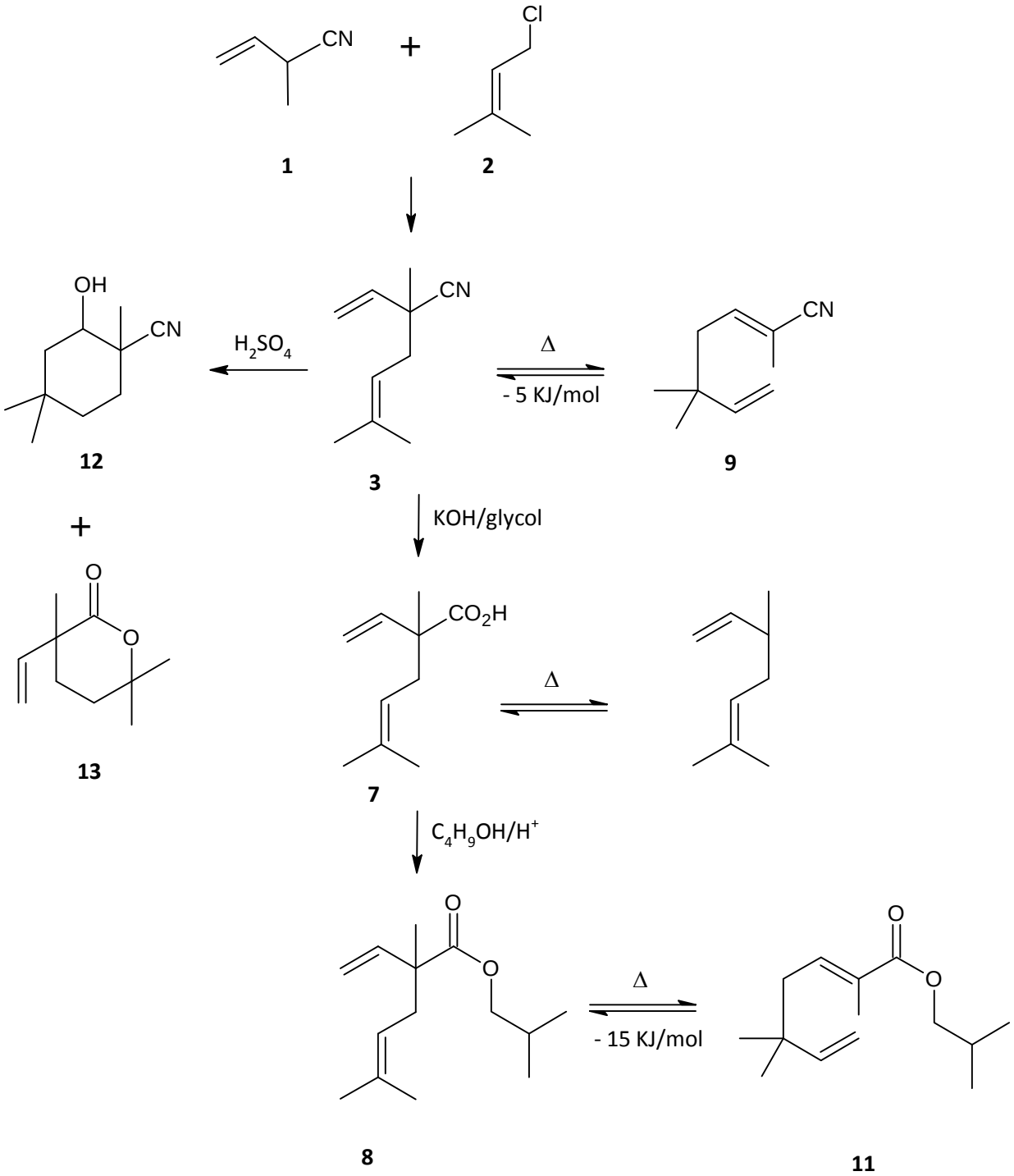


Figure 34: Scheme for achieved synthesis

6. Future Work

As expected in investigation and laboratory works of optimization and synthesis of new flavour compounds the work is not finished. The new compounds need to be presented to the partners of this project; also the potential fragrances need a further optimization.

In the case of Neronil **3,** an intensive research of this compound was initiated in this project. The optimization of Neronil is finished at this time, but its synthesis is still needed as it is the main compound of this work and the related compounds are produced from this product.

The results of the hydrolysis of the acid **7** under basic conditions have been very satisfying and for this reason an extra optimization of this synthesis is also not needed. On the other hand the optimization of synthesis of the products **12** and **13**, formed by mixing Neronil with sulfuric acid, is essential. It is necessary to isolate each product and to analyse if they could be potential flavours compounds for the project.

An optimization of the ester **8** is also not required in the future but a better isolation of the product by distillation is vital. Additionally investigations of the esterification of the acid **7** can be implemented but with different alcohols. For example with methanol in order to produce 2,5-dimethyl-2-vinyl-4-hexenoic acid methyl ester.

This ester can have a better performance in order to synthesise the respective Cope-rearrangement product, because it should have a lower steric hindrance. As already seen the optimization of the Cope product **9** from Neronil and the Cope product **11** from ester is very complicated. It is known that Cope-rearrangements can be very successful when adding a catalyst, like palladium dichloride, to the reaction in order to reduce the temperature and to achieve a complete conversion of the educts. Therefore this way could be more promising.

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Attachments

Annex 1 – GC-MS Results

This annex contains examples of one GC chromatogram and one MS spectrum from the experiments realized in this work and is organised by the main product from each reaction:

Annex 2 – NMR- spectra Results

Enclose the decisive NMR spectrums to identify the structure of the new compounds synthesised in this work:

Annex 1 – GC-MS Results

- Neronil

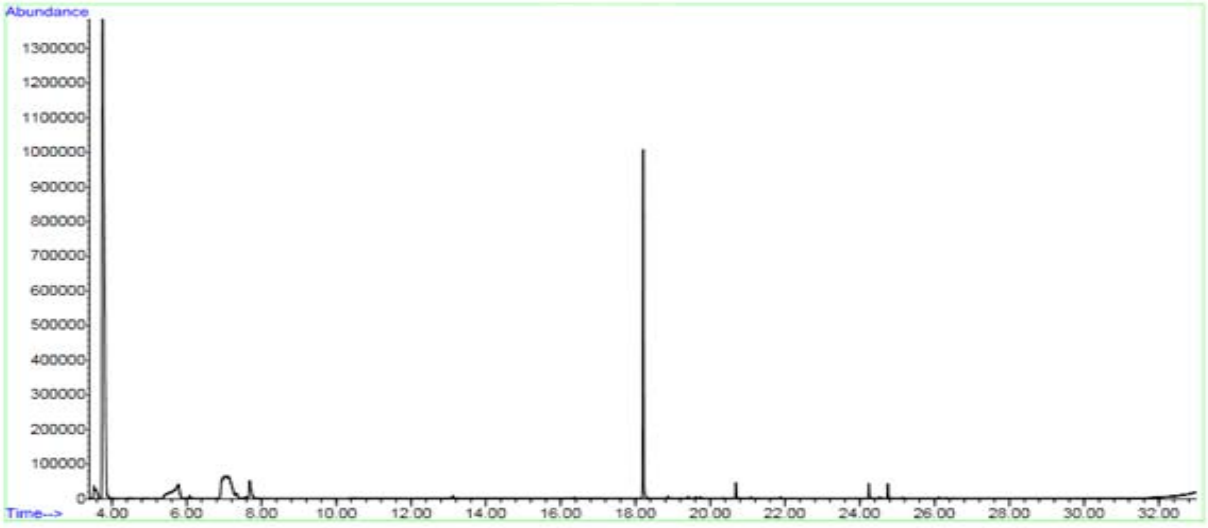


Figure 35: GC chromatogram during the experiment DWN5

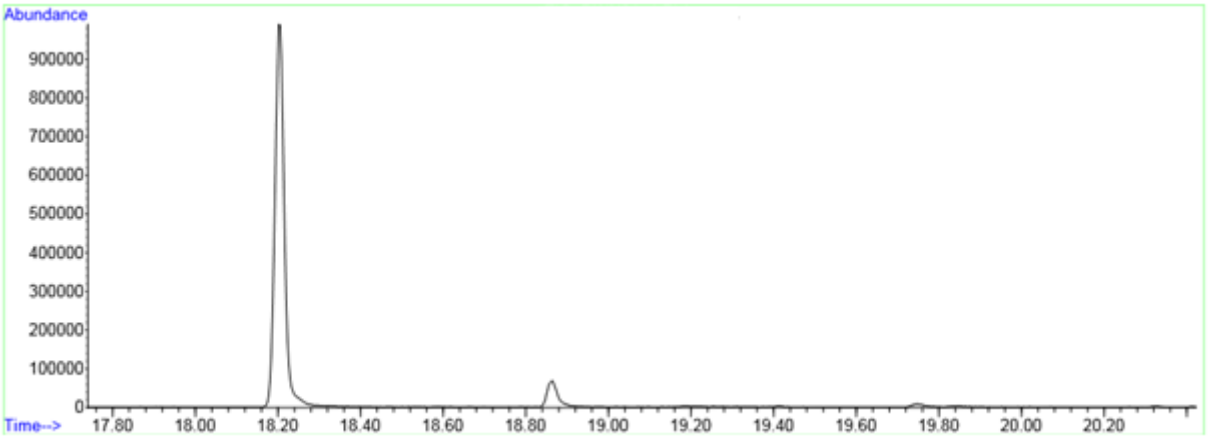


Figure 36: GC chromatogram after work-up of experiment DWN31

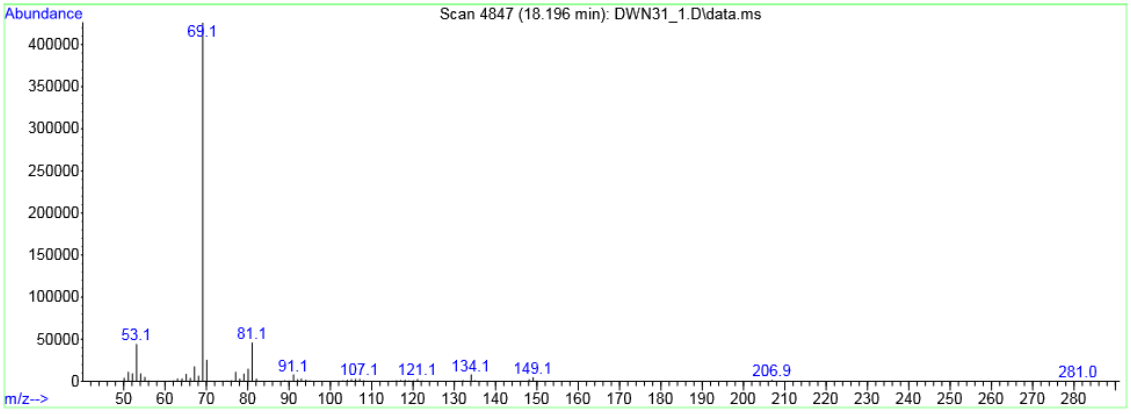


Figure 37: Mass spectrum of Neronil in experiment DWN31

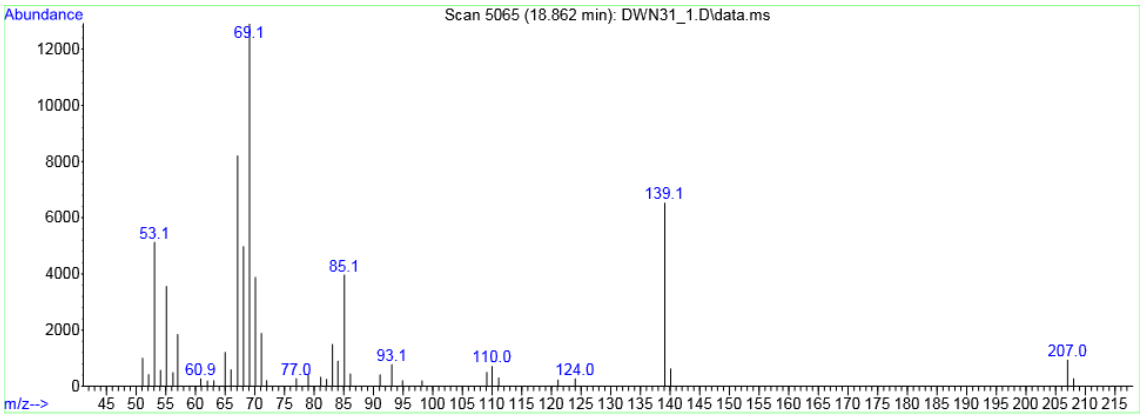


Figure 38: Mass Spectrum of ether in experiment DWN31

- Acid

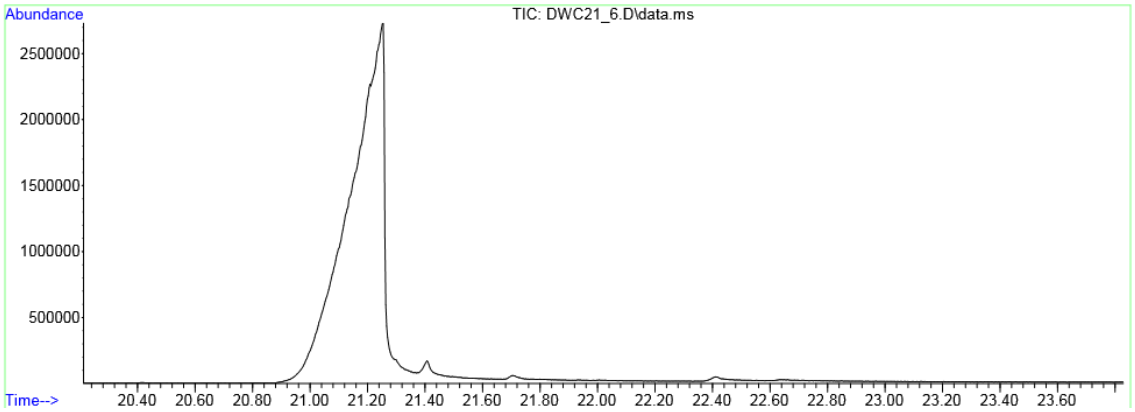


Figure 39: GC chromatogram of the acid in experiment DWC21

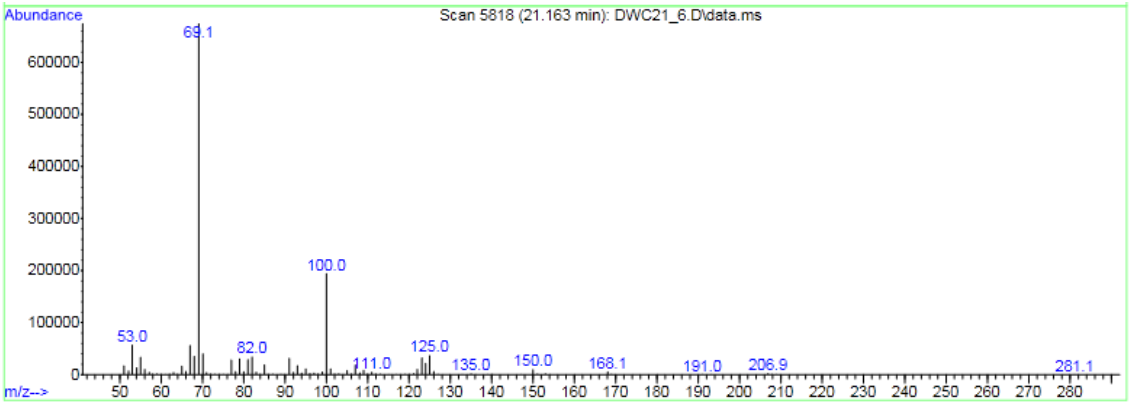


Figure 40: Mass spectrum of acid in experiment DWC21

- Cyclohexanol

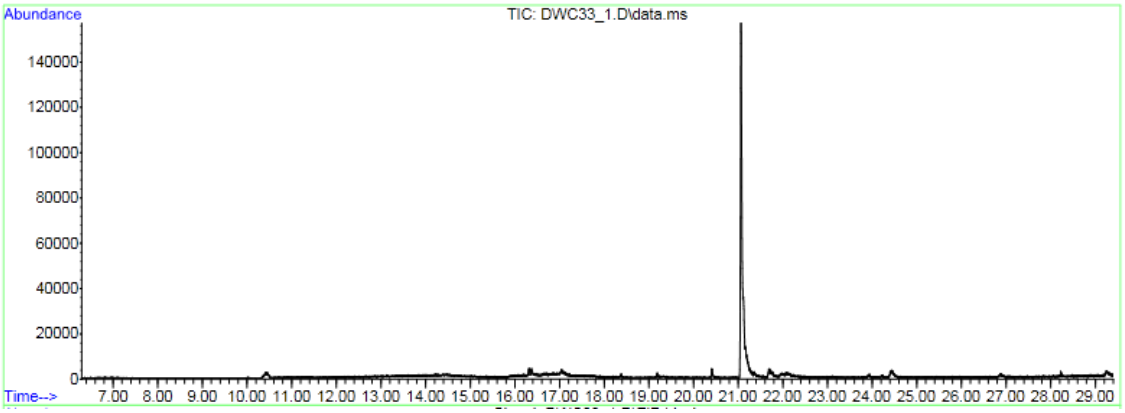


Figure 41: GC chromatogram of cyclohexanol in experiment DWC33

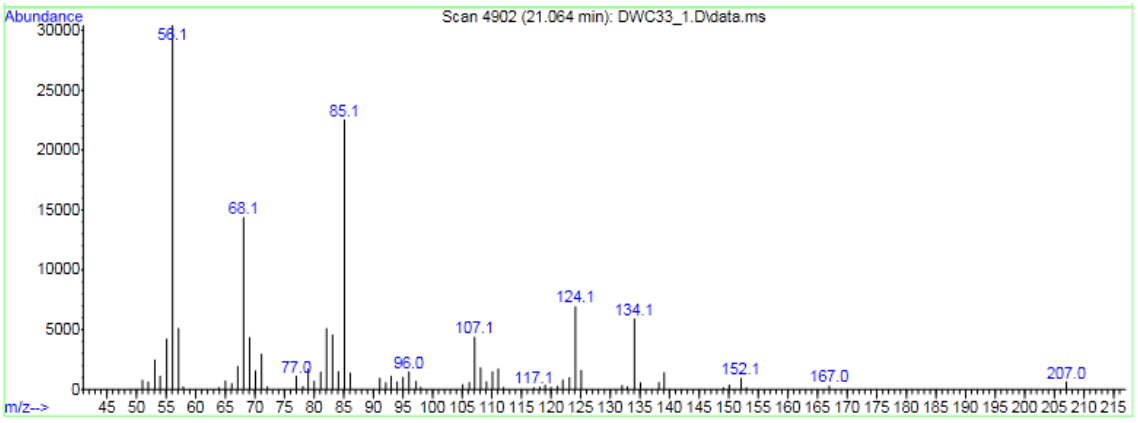


Figure 42: Mass spectrum of cyclohexanol in experiment DWC33

- Ester

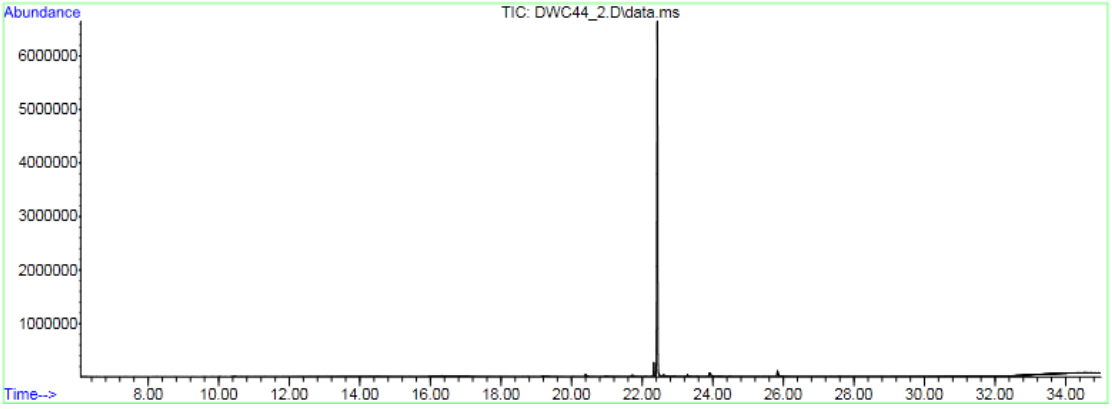


Figure 43: GC chromatogram of the ester after work-up in experiment DWC44

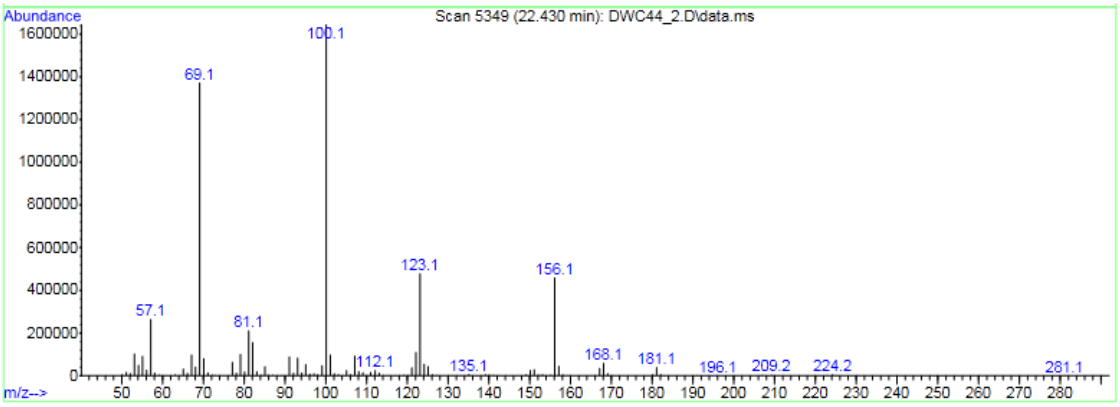


Figure 44: Mass spectrum of the ester in experiment DWC44

- Cope-rearrangement of Neronil

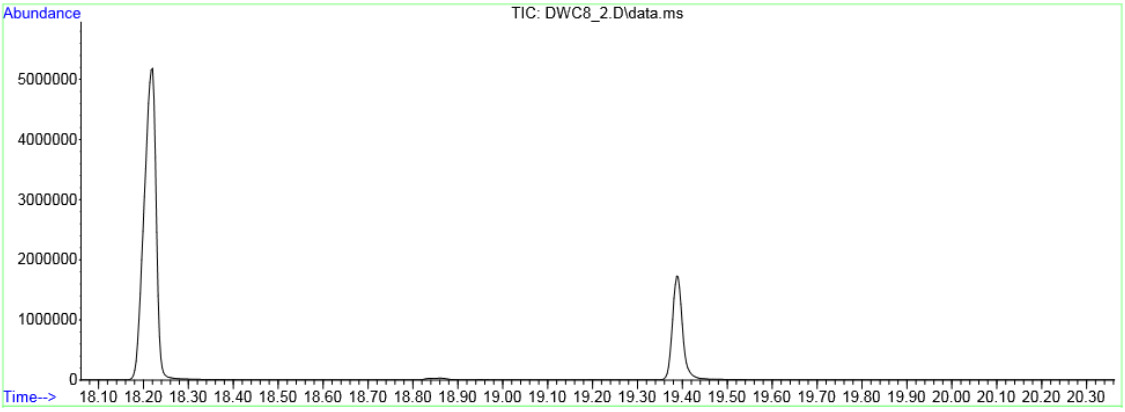


Figure 45: GC chromatogram of the Neronil cope product in experiment DWC8

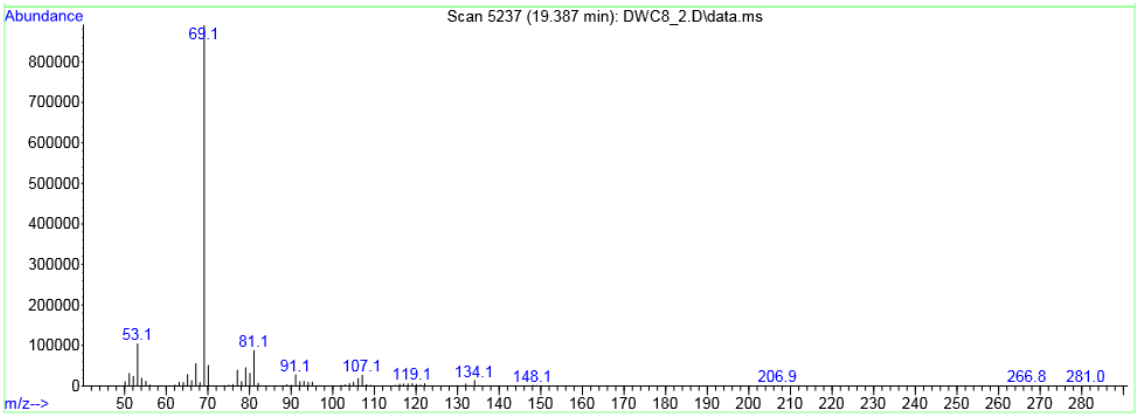


Figure 46: Mass spectrum of the Neronil cope product in experiment DWC8

- Cope-rearrangement of ester

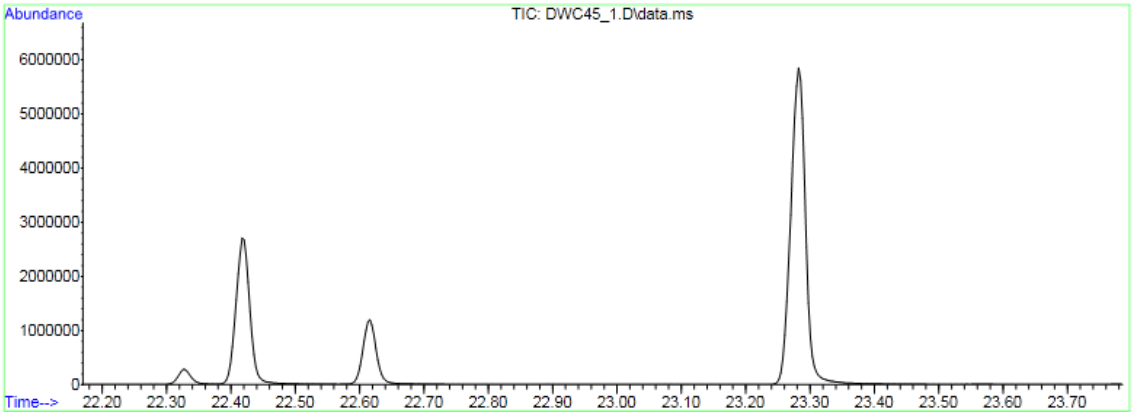


Figure 47: GC chromatogram of the ester cope product in experiment DWC45

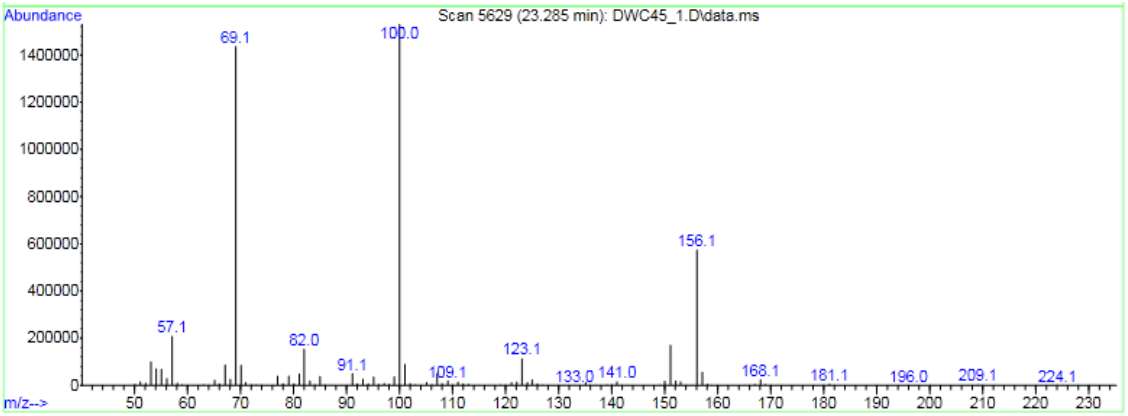
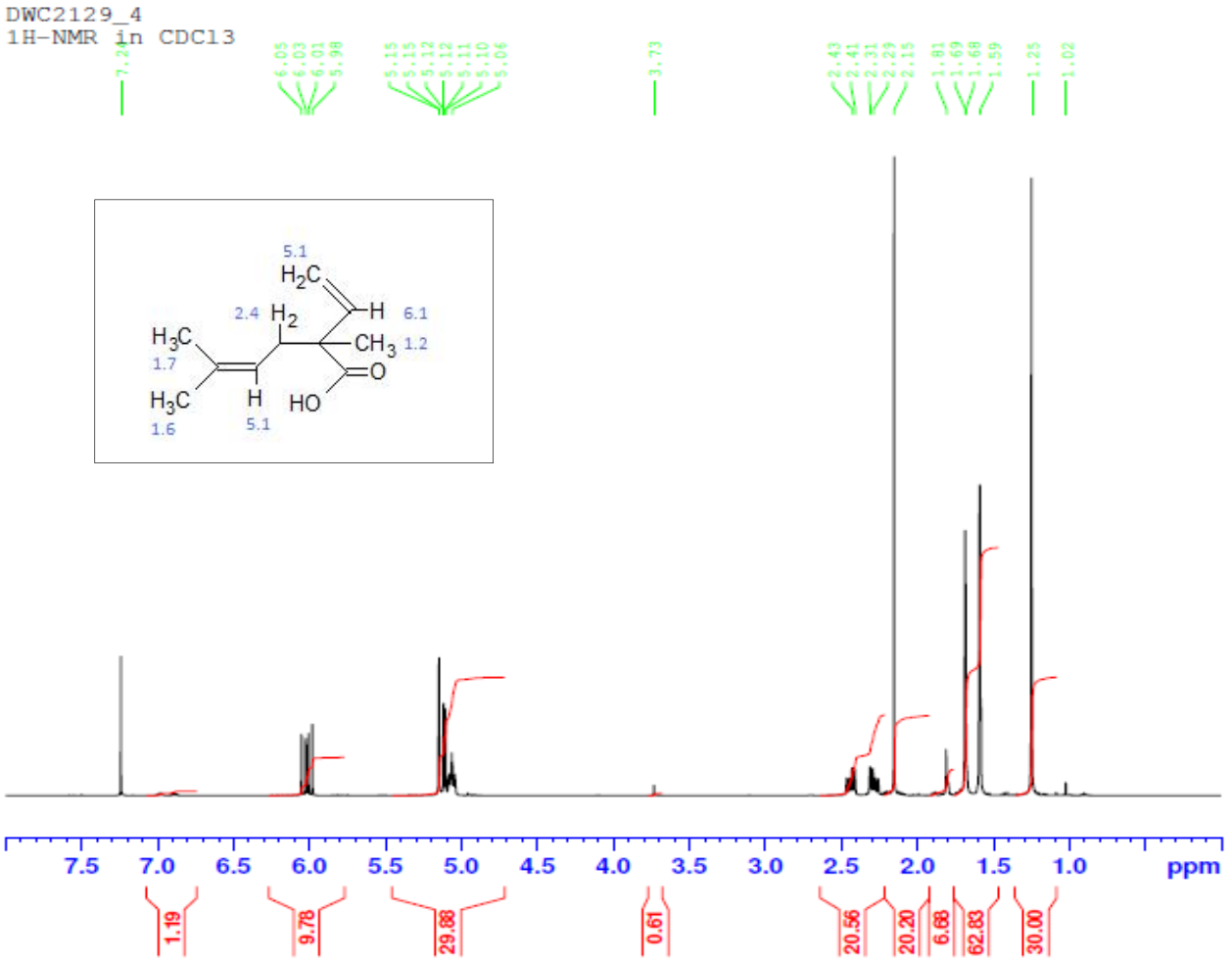


Figure 48: Mass spectrum of the ester cope product in experiment DWC45

Annex 4 – NMR- spectra Results

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DS                       2
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FIDRES             0.073360 Hz
AQ                 6.8157439 sec
RG                     101
DW                 104.000 usec
DE                   6.50 usec
TE                  298.2 K
D1           10.00000000 sec
TD0                      1

====== CHANNEL f1 ======
SFO1          400.2316132 MHz
NUC1                    1H
P1                   13.50 usec
PLW1          17.98900032 W

F2 - Processing parameters
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SF            400.2300206 MHz
WDW                     EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
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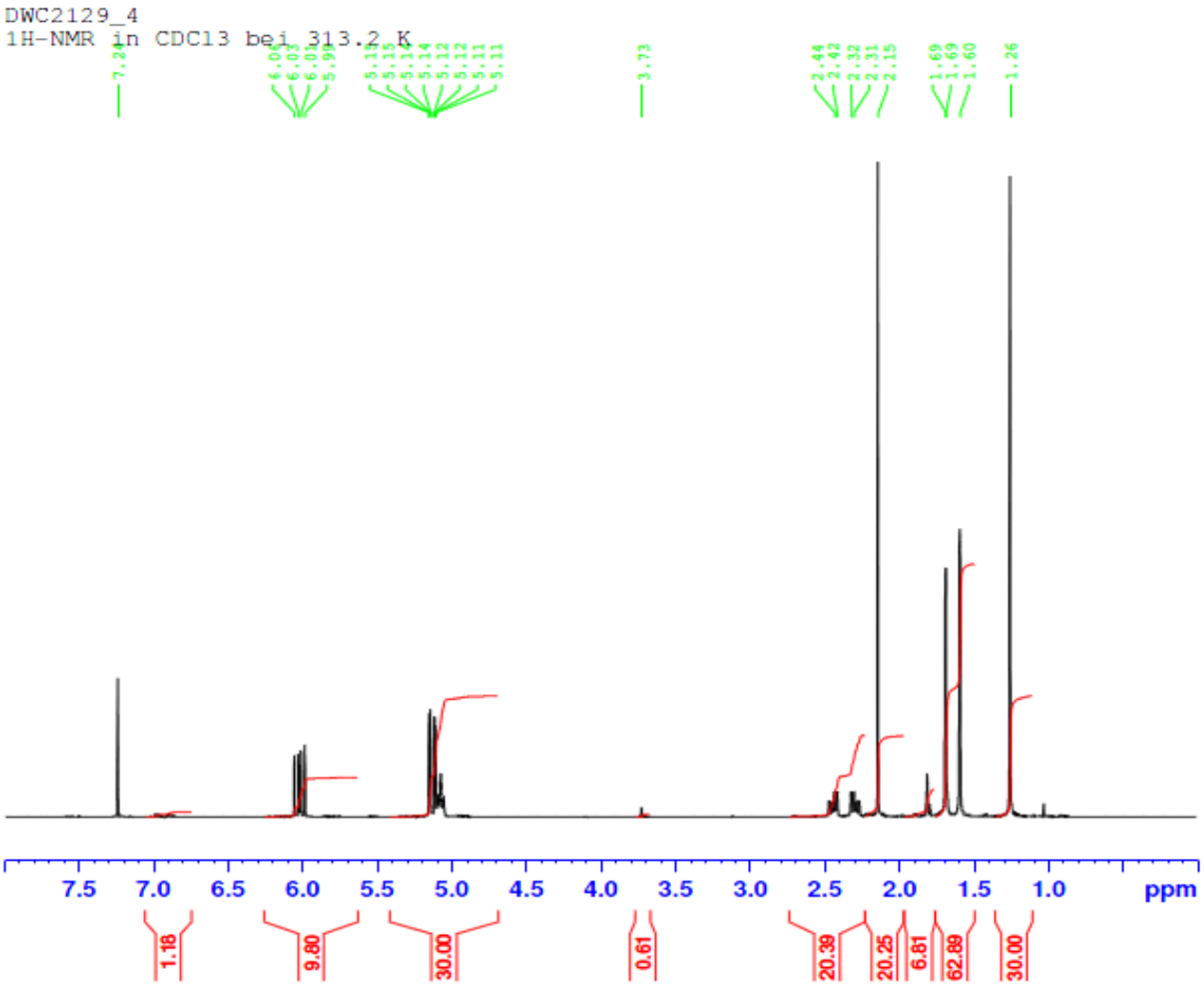
Figure 49: ^{1}H-NMR (25 °C) from acid after distillation from DWC2129 **[59]**



BRUKER

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FIDRES            0.073360 Hz
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TE                  313.2 K
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TD0                       1

======== CHANNEL f1 ========
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NUC1                    1H
P1                  13.50 usec
PLW1           17.98900032 W

F2 - Processing parameters
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SF             400.2300200 MHz
WDW                     EM
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LB                  0.30 Hz
GB           0
PC                  1.00
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Figure 50: ^{1}H-NMR (40 °C) from acid after distillation from DWC2129

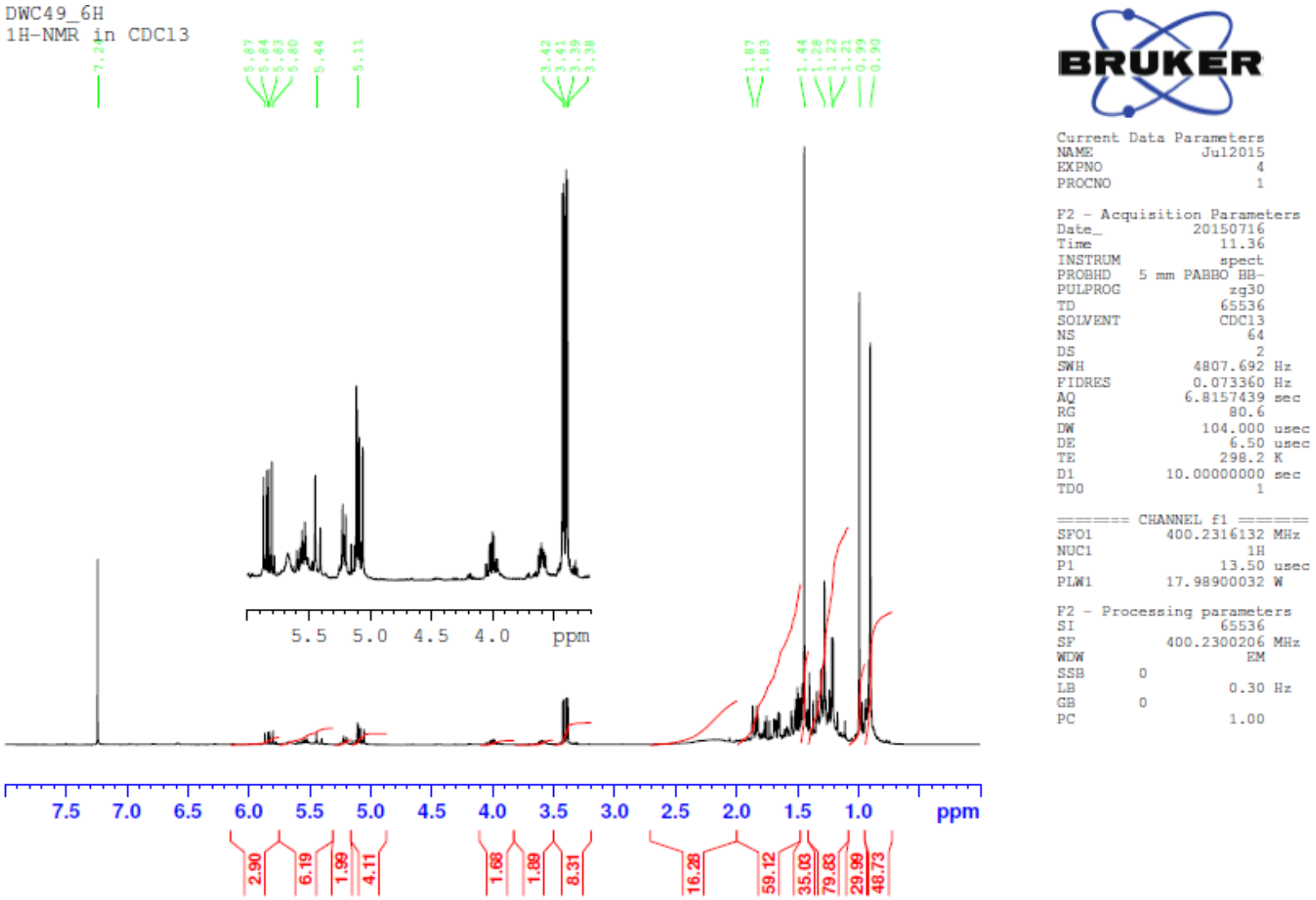
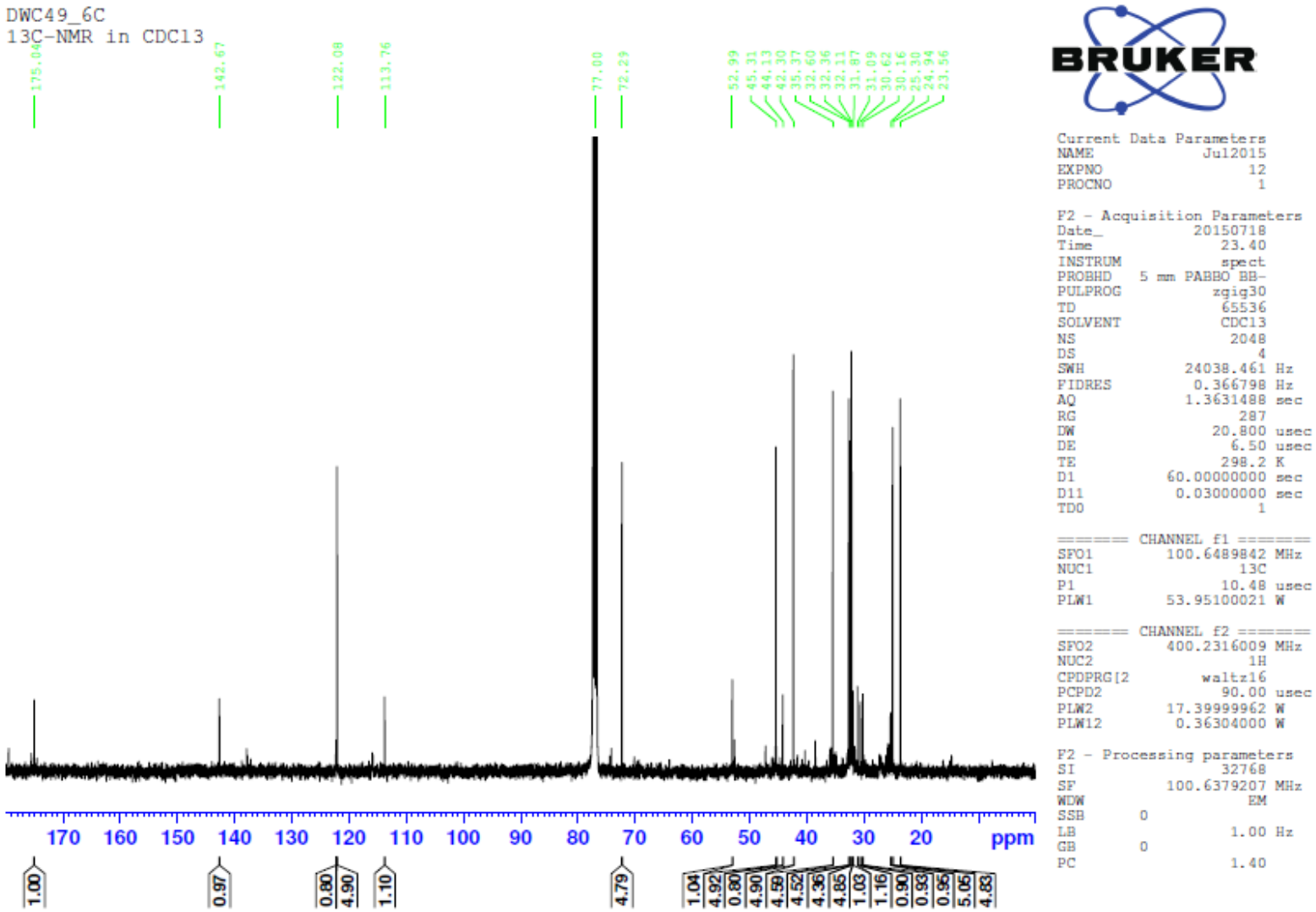


Figure 51: ^{1}H-NMR from the mixture of cyclohexanol and lactone after work up from DWC49



BRUKER

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DS                          4
SWH                24038.461 Hz
FIDRES             0.366798 Hz
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RG                        287
DW                   20.800 usec
DE                    6.50 usec
TE                    298.2 K
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D11                0.03000000 sec
TD0                         1

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NUC1                      13C
P1                      10.48 usec
PLW1              53.95100021 W

====== CHANNEL f2 =======
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PCPD2                   90.00 usec
PLW2              17.39999962 W
PLW12              0.36304000 W

F2 - Processing parameters
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SF                100.6379207 MHz
WDW                        EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
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Figure 52: ^{13}C-NMR from the mixture of cyclohexanol and lactone after work up from DWC49

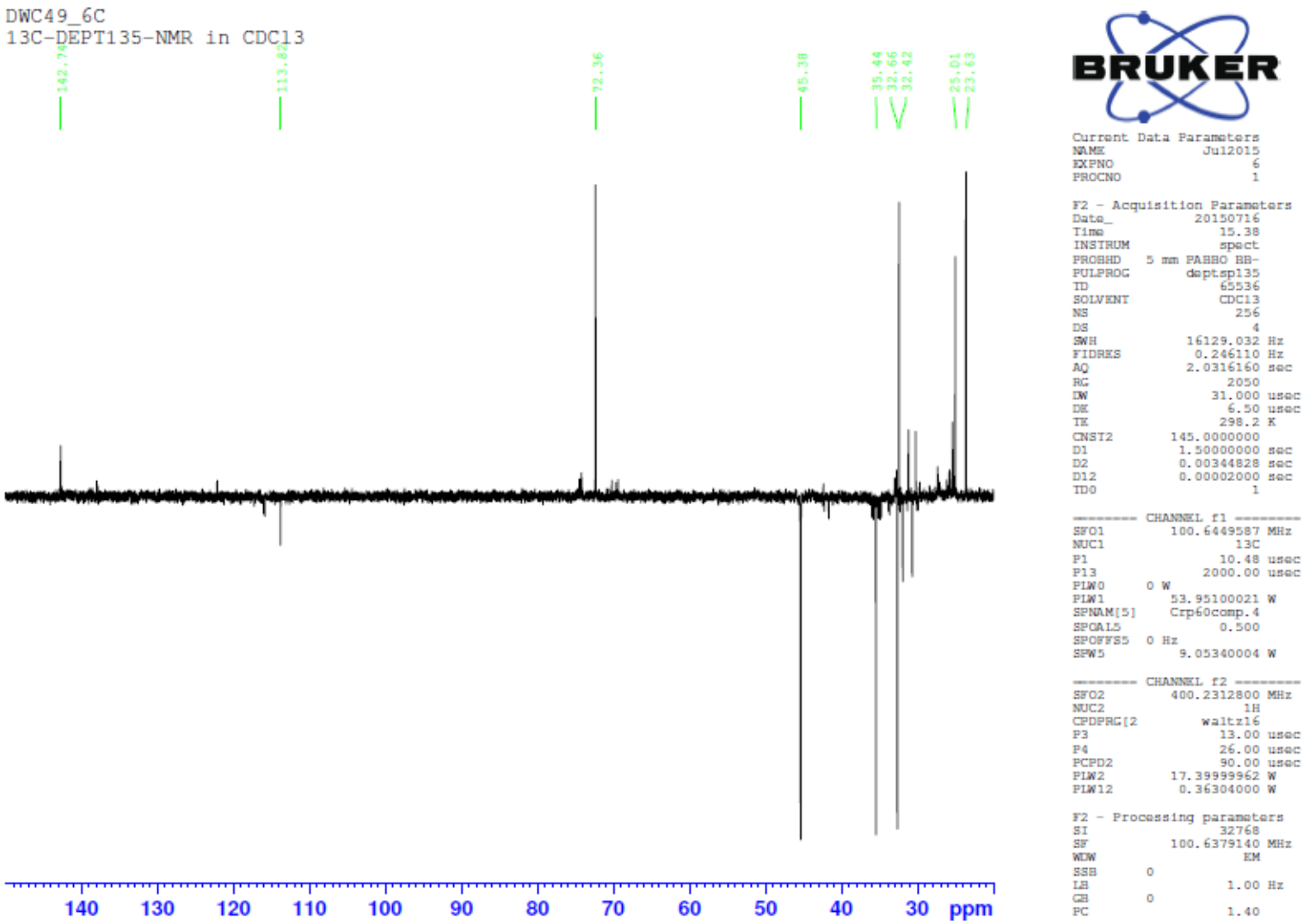


Figure 53: ^{13}C-DEPT-NMR from the mixture of cyclohexanol and lactone after work up from DWC49

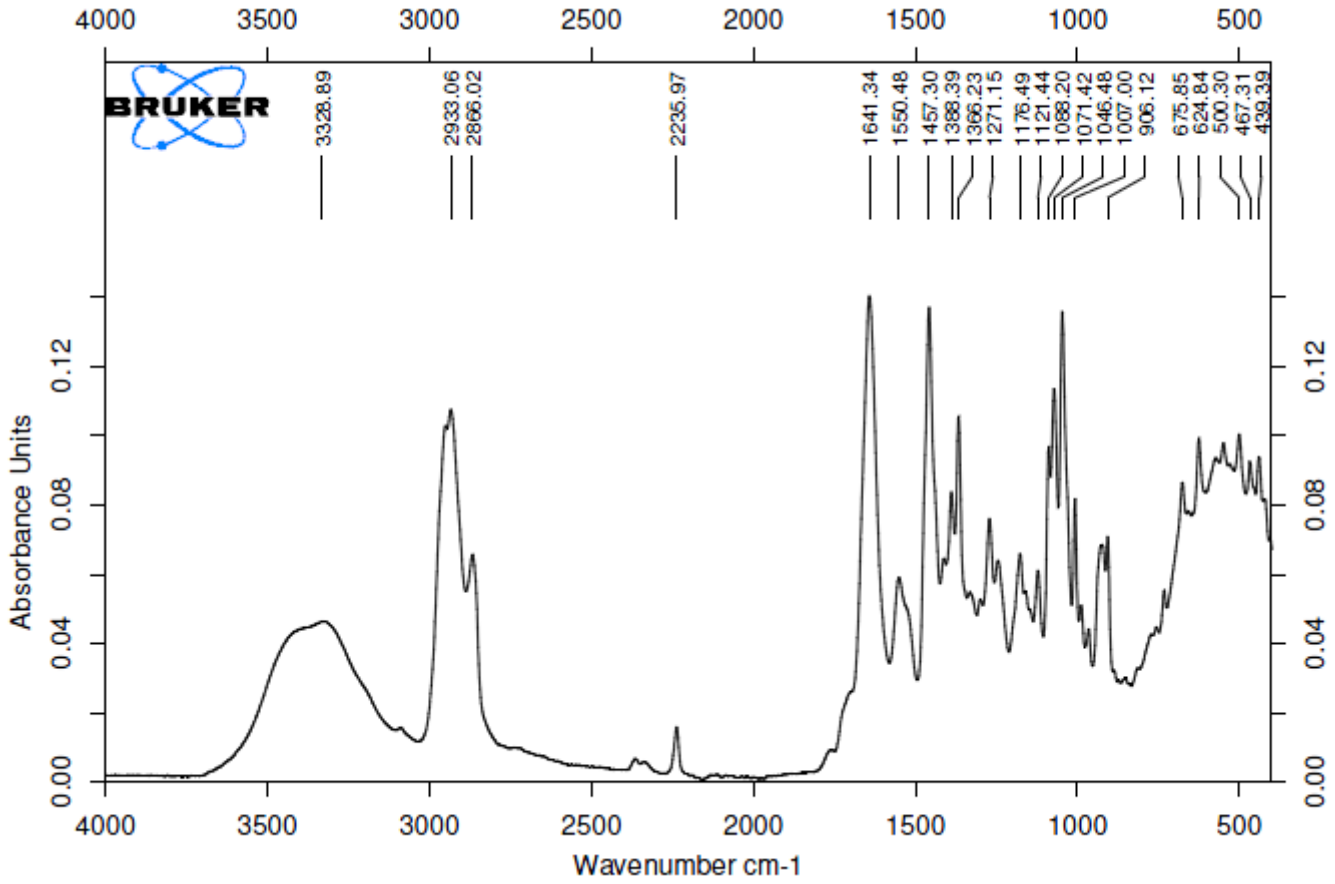
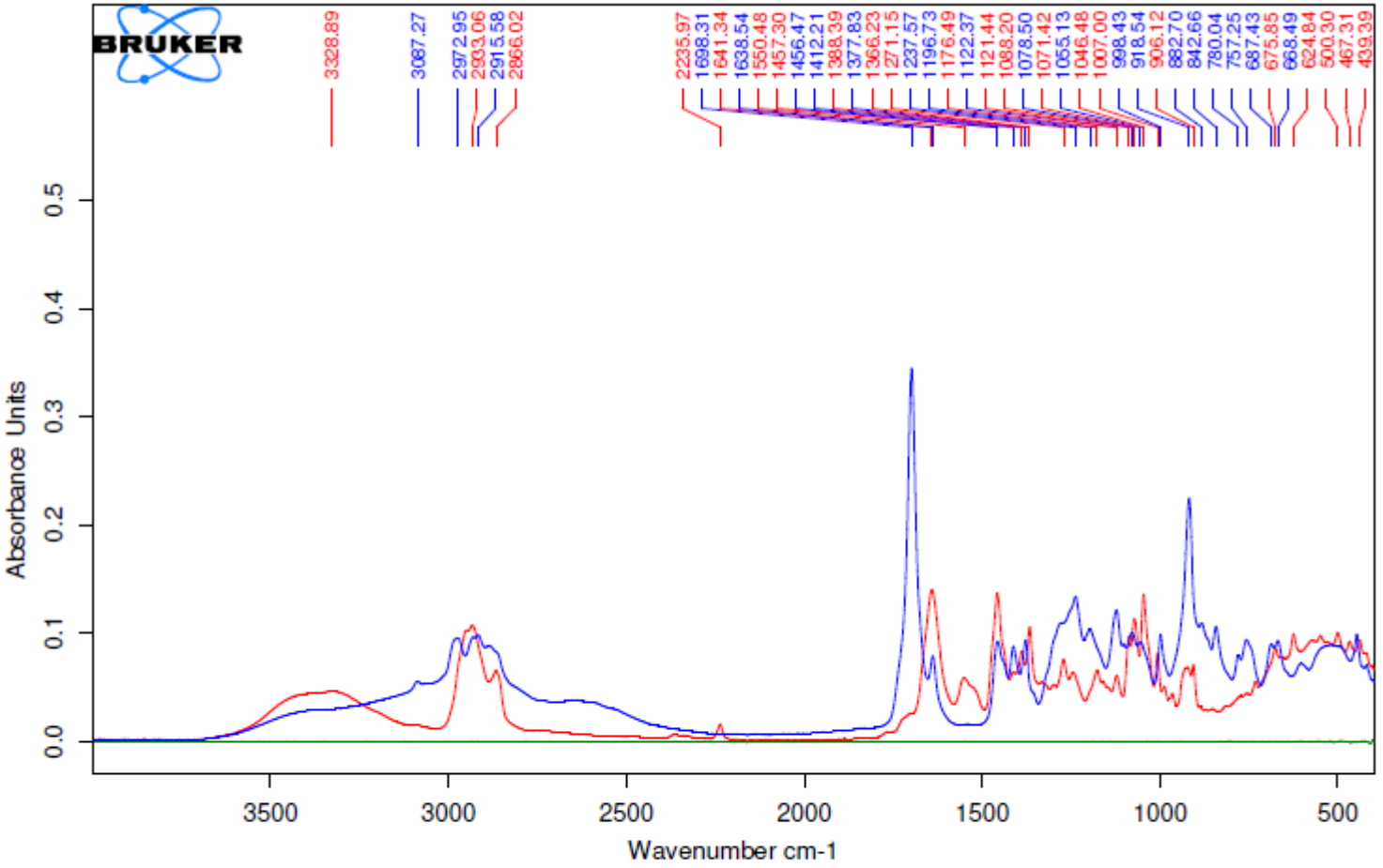


Figure 54: IR-NMR from the mixture of cyclohexanol and lactone after work up from DWC49



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D:\Data\schz\Prof Rödel\15-07-15\Säure-PATR-15-07-15.0	Säure	Platinum-ATR Diamond, RT-DLaTGS	15.07.2015
D:\Data\schz\Prof Rödel\15-07-15\Probe-PATR-15-07-15.0	Probe	Platinum-ATR Diamond, RT-DLaTGS	15.07.2015

Figure 55: IR-NMR from the mixture of cyclohexanol and lactone and acid

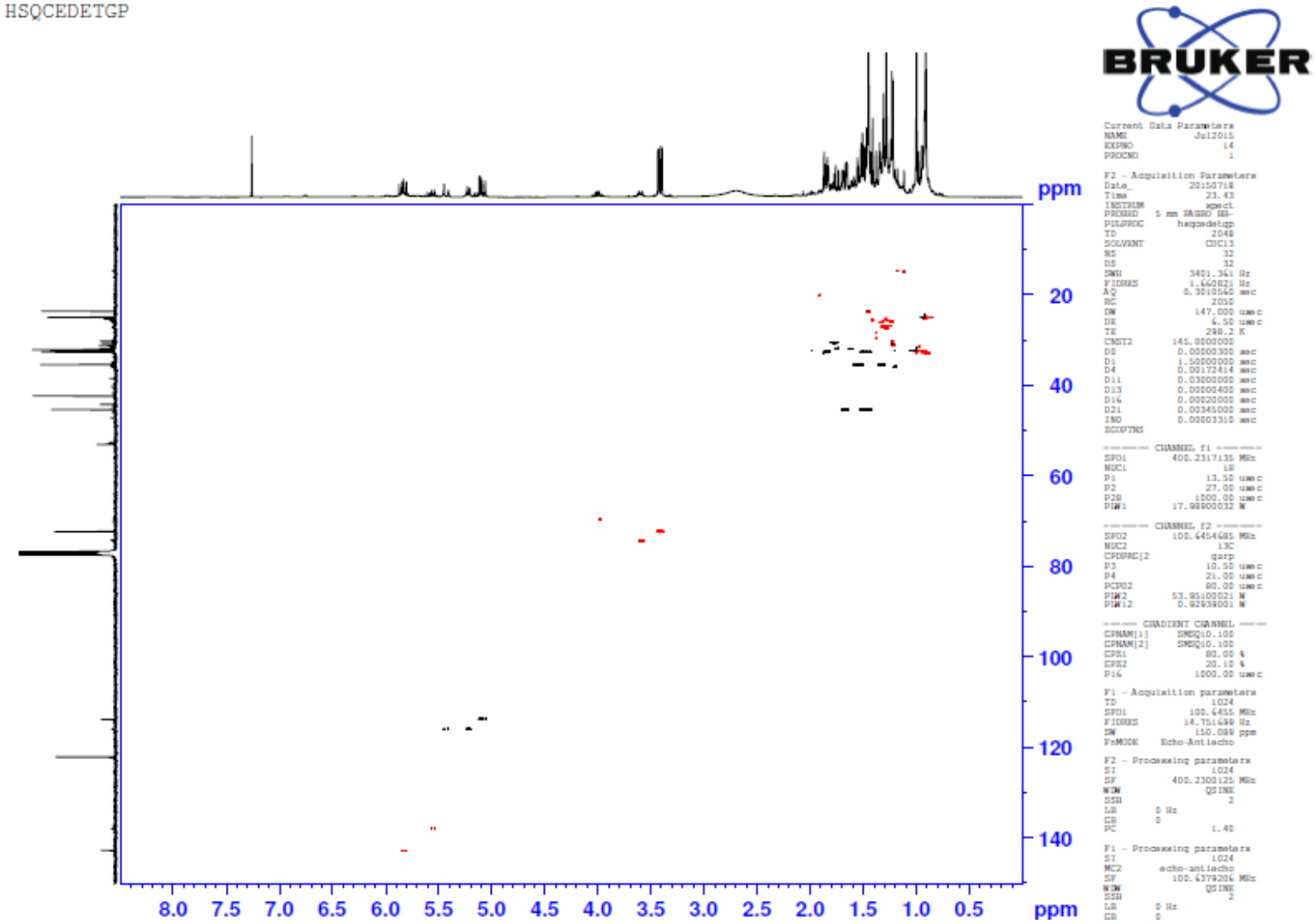
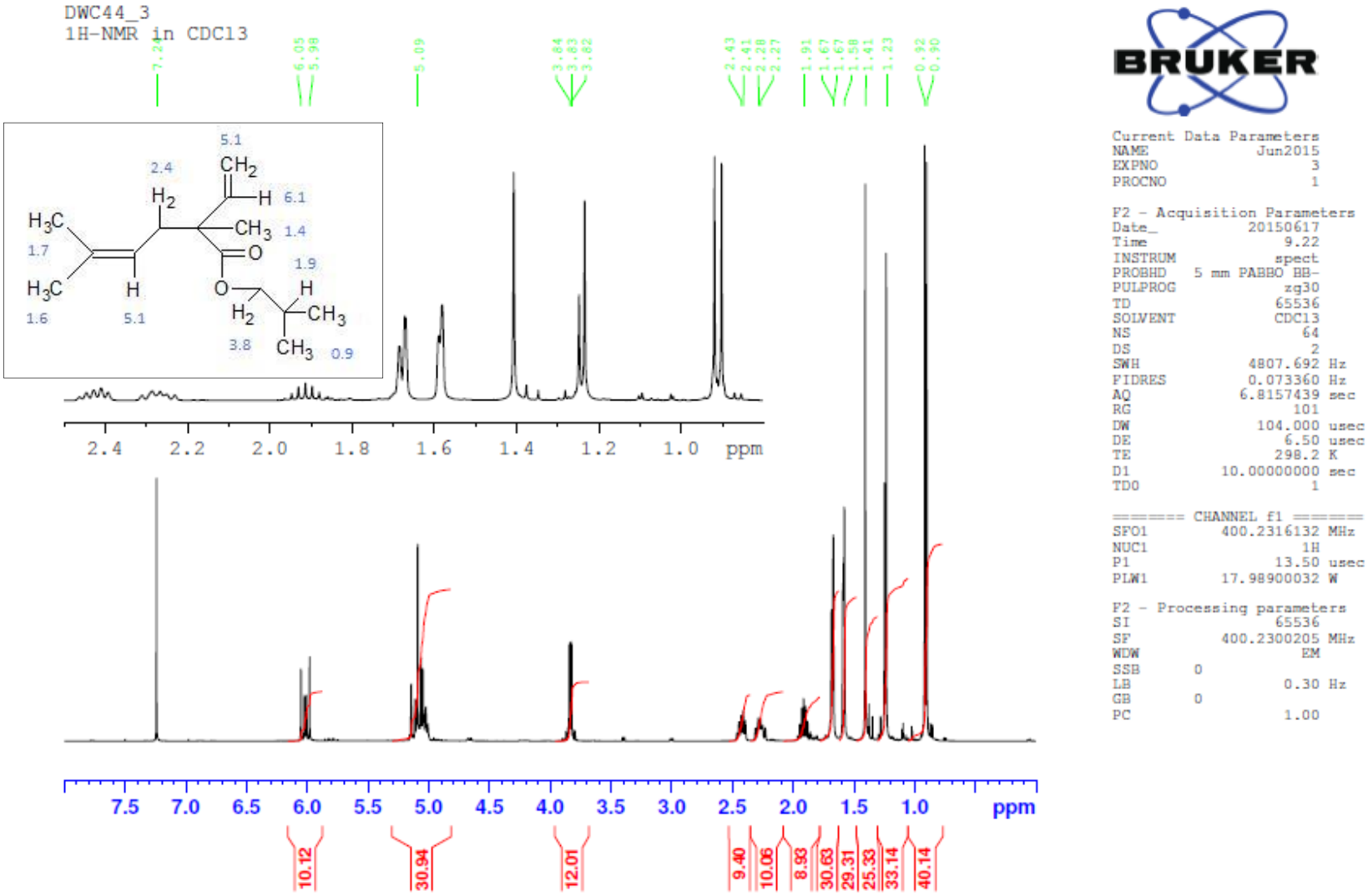


Figure 56: HSQCEDETGP-NMR from the mixture of cyclohexanol and lactone after work up from DWC49

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AQ                 6.8157439 sec
RG                        101
DW                  104.000 usec
DE                    6.50 usec
TE                   298.2 K
D1                10.00000000 sec
TD0                         1

====== CHANNEL f1 ======
SFO1          400.2316132 MHz
NUC1                     1H
P1                   13.50 usec
PLW1          17.98900032 W

F2 - Processing parameters
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SF            400.2300205 MHz
WDW                        EM
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LB                    0.30 Hz
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PC                    1.00
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Figure 57: ^{1}H-NMR (25 °C) from ester after workup from DWC44

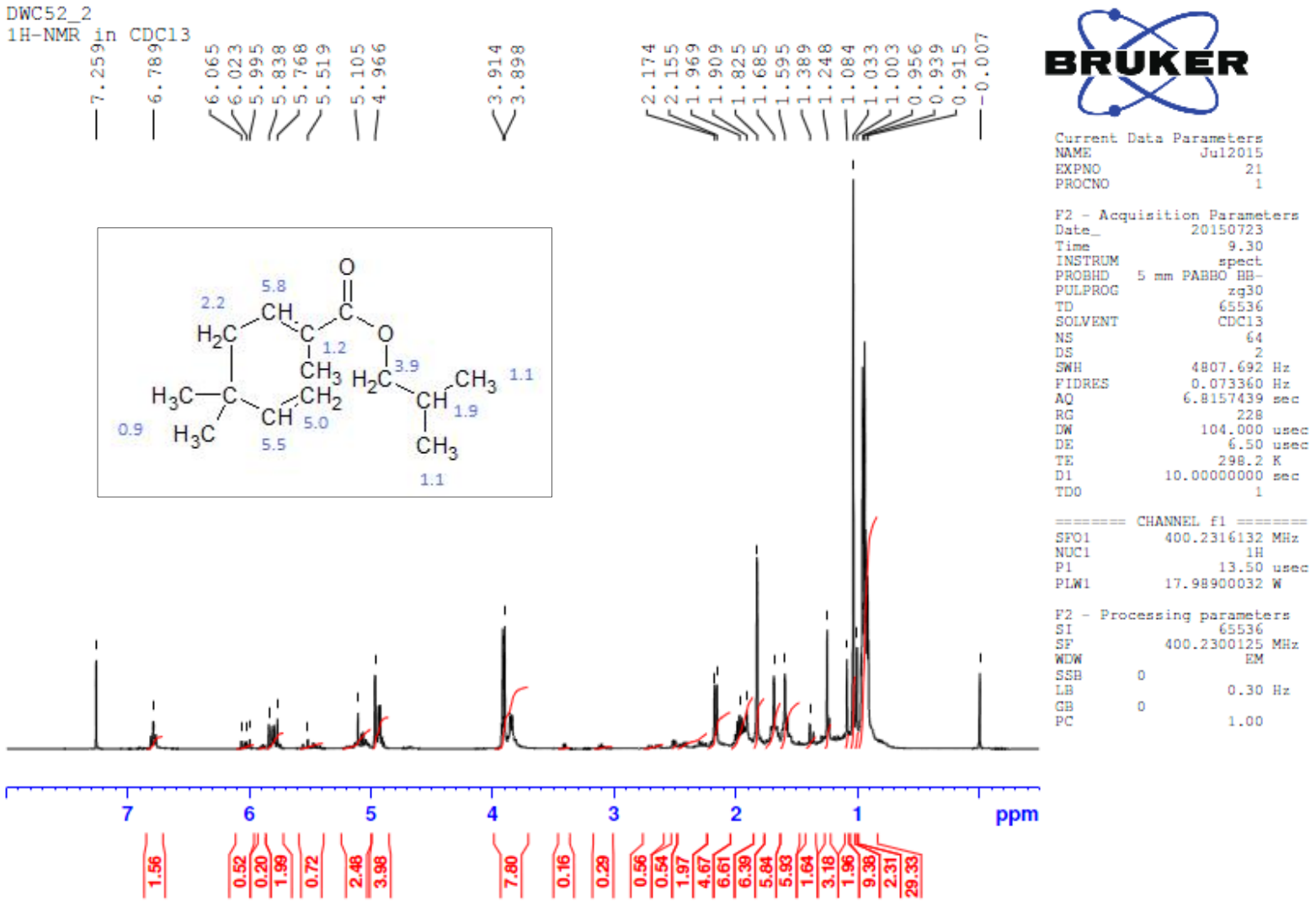
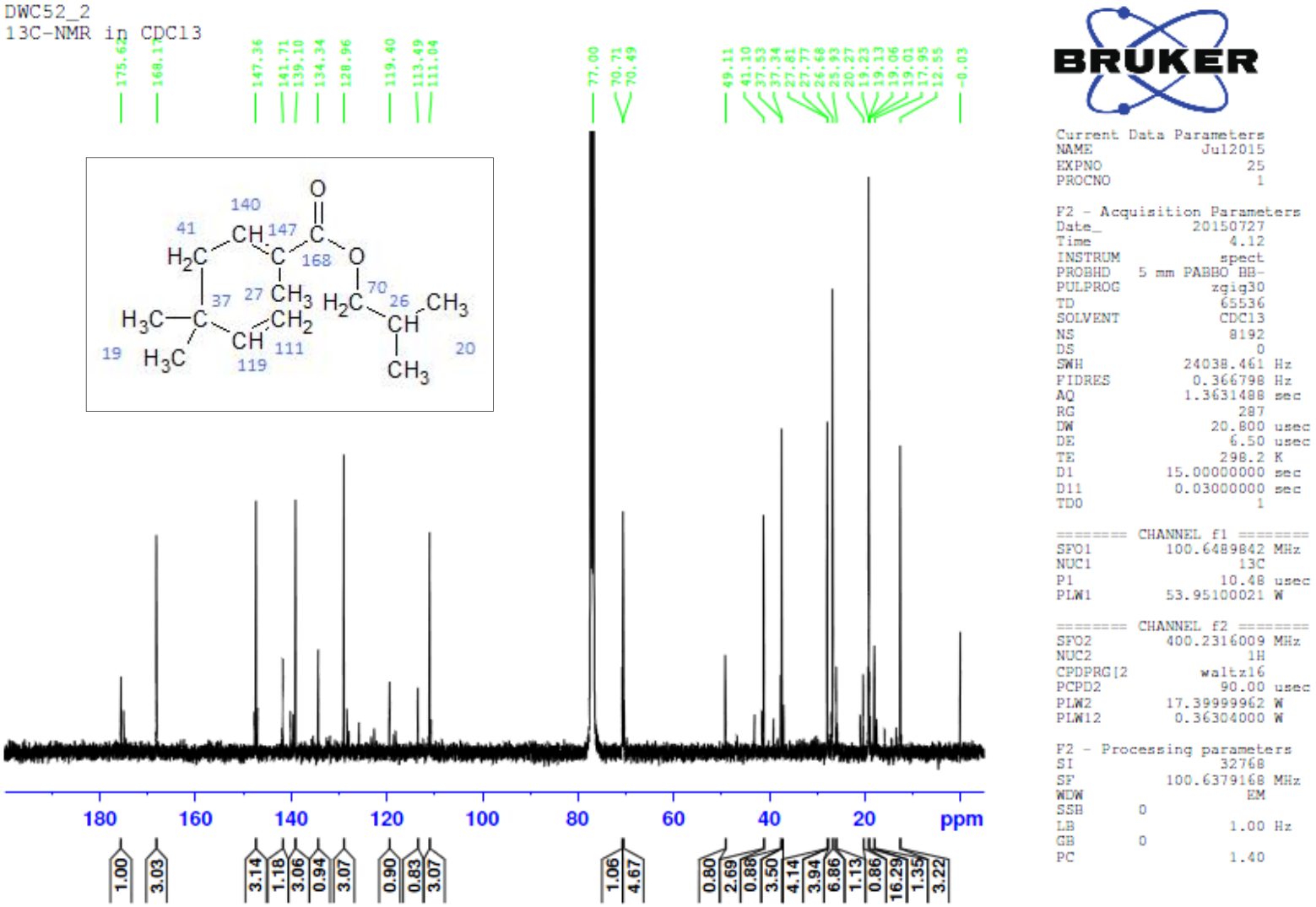


Figure 58: ^{1}H-NMR (25 °C) from ester cope product after workup from DWC52

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NS                       8192
DS                          0
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631488 sec
RG                        287
DW                   20.800 usec
DE                    6.50 usec
TE                    298.2 K
D1                15.00000000 sec
D11                0.03000000 sec
TD0                         1

======== CHANNEL f1 =======
SFO1             100.6489842 MHz
NUC1                      13C
P1                     10.48 usec
PLW1              53.95100021 W

======== CHANNEL f2 =======
SFO2             400.2316009 MHz
NUC2                      1H
CPDPRG[2               waltz16
PCPD2                  90.00 usec
PLW2              17.39999962 W
PLW12              0.36304000 W

F2 - Processing parameters
SI                        32768
SF               100.6379168 MHz
WDW                         EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

Figure 59: ^{13}C-NMR (25 °C) from ester cope product after workup from DWC52

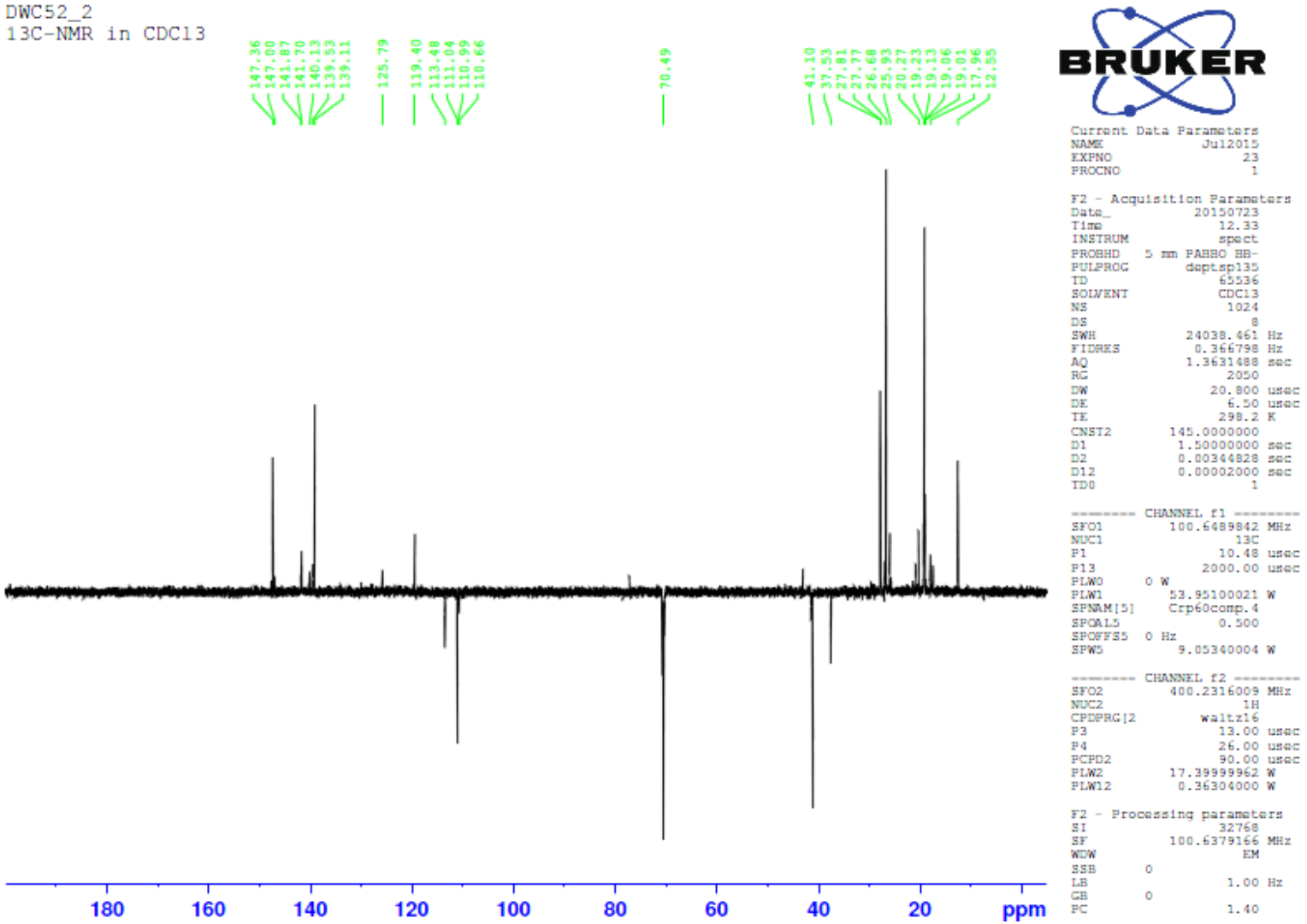

Figure 60: ^{13}C-DEPT-NMR (25 °C) from ester cope product after workup from DWC52

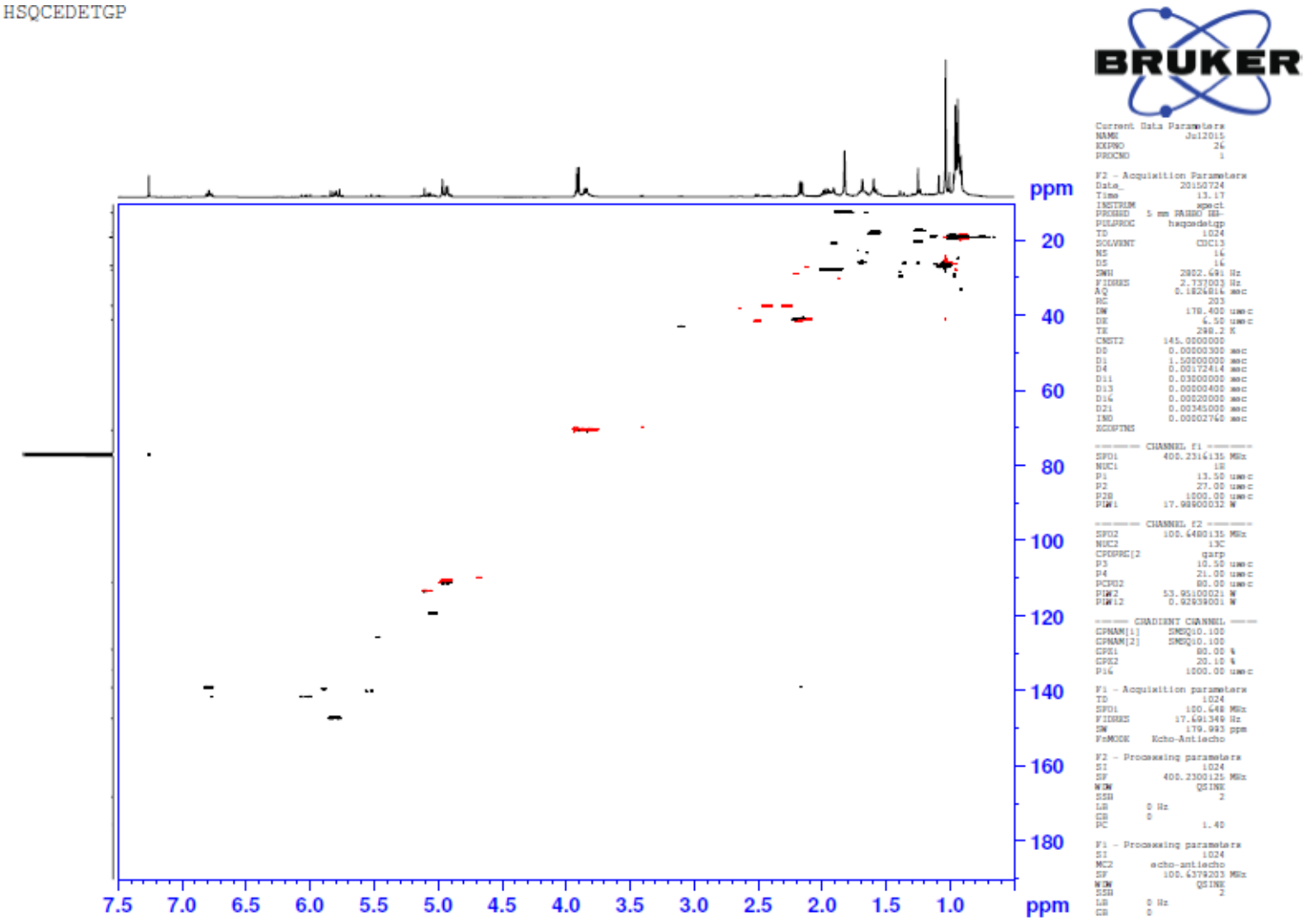

Figure 61: HSQCEDETGP-NMR (25 °C) from ester cope product after workup from DWC52